THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

1943 — 1983

FORTY YEARS OF SERVICE TO CANCER PATIENTS

7 Overlea Boulevard
Toronto, Ontario M4H 1A8
(416) 423-4240

M.A. MEIGHEN, Q.C., Chairman
Dr. J.W. MEAKIN, Executive Director
R.D. GRAY, Secretary-Treasurer

April 1983

DRUG SERVICE FOR CANCER PATIENTS

Dear Colleague:

The Ontario Cancer Treatment and Research Foundation provides designated chemotherapeutic agents free of charge to cancer patients who are residents of Ontario and are at home under the care of their doctors. We have undertaken this program to assist those patients who are finding the cost of therapy with expensive drugs beyond their financial resources.

Patients who are eligible for government-supported or private drug insurance plans must use these methods rather than the Foundation's Drug Service to cover their costs.

In case you have patients who would benefit from the Foundation's Drug Service, I urge you to review the information included with this letter. I hope that you will find this program useful in the care of your patients.

Sincerely,

J. William Meakin, M.D., M.A., F.R.C.P. (C).,
Executive Director

DRUG SERVICE FOR CANCER PATIENTS

ELIGIBILITY OF PATIENTS

This service is restricted to patients who reside in Ontario, and it is intended for ambulatory patients. It should be noted that the injectable drugs on the list are covered as an insured service at our clinics, or in the outpatient department of certain hospitals. These injectables will only be covered by the Drug Service where these particular facilities are not available to the patient.

The Foundation's Drug Service does not cover patients who are over 65 years of age nor those receiving any form of social assistance, since these patients are eligible for the Drug Benefit Plan of the Ministry of Health. Prescriptions for these drugs can be filled at a local pharmacy and should be billed directly to the Drug Benefit Plan rather than the Foundation. A physician may request authorization for drugs not included in the Drug Benefit Formulary on behalf of patients eligible for the Plan by telephoning the Ontario Drug Benefit, Special Authorization, Ministry of Health. Collect calls will be accepted through telephone number (416) 965-6699. The authorization number must be provided to the pharmacy filling the prescription. Patients with private drug insurance are expected to recover drug costs from their insurer.

PROCEDURE FOR PRESCRIBING

Drugs can be supplied only if the attending doctor completes special prescription forms which are available from this office. Each prescription must specify the generic name of the drug, the dosage and frequency of administration, and be signed by the prescribing doctor. Certain minimal information about the patient is requested for statistical purposes, since a record of these prescriptions is kept. Please ensure that this information is provided in legible form — preferably typed. The completed form should be mailed to the nearest Foundation clinic (see back page); **prescriptions can only be filled at the hospital pharmacies associated with these clinics. Accounts for prescriptions filled at pharmacies other than those authorized by the Foundation will not be accepted for payment.** Please allow seven to ten days for processing.

QUANTITY TO BE DISPENSED

Each drug will be limited to a one-month supply, unless special circumstances exist. The first supply will be mailed to the physician so that he or she can give the patient proper instructions concerning its use. Repeat prescriptions will be mailed directly to the patient, unless the drug must be administered by injection. Hormones for replacement therapy and those used in long-term therapy of diseases, like carcinoma of the prostate, will be supplied in amounts sufficient for two or three months.

AGENTS AVAILABLE

The list of medications is on the following page. Please note that prednisone is no longer available through the Drug Service. The cost of this drug is so low that there would be very few patients who would not be able to afford to pay for this drug. However if the cost of the drug would place an unusual burden on the patient, it may be supplied by special arrangement. In addition to the list of medications on the following pages, there are also several other drugs which are used infrequently or which, because of their expense should only be used if a less expensive product is unsuitable; the physician should contact the Director of the Clinic for authorization of drugs in this category.

PAIN-RELIEVING DRUGS AND SEDATIVES

The Ontario Division of the Canadian Cancer Society provides certain drugs in this category. **To obtain these,** the physician should apply to the local branch of the Society, **not** to the Foundation.

MEDICATIONS AVAILABLE FROM THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION

CYTOTOXIC ANTINEOPLASTIC AGENTS

Amethopterin (Methotrexate)
Bleomycin (Blenoxane)
Busulfan (Myleran)
Chlorambucil (Leukeran)
Cyclophosphamide (Cytoxan, Procytox)
Cytarabine (Cytosar)
Dactinomycin (Cosmegen)
Daunorubicin (Cerubidine, Daunomycin)
Doxorubicin (Adriamycin)
Fluorouracil
Hydroxyurea (Hydrea)
Lomustine, CCNU (CeeNU)
Mechlorethamine, Nitrogen Mustard (Mustargen)
Melphalan (Alkeran)
Mecaptopurine (Purinethol)
Mitomycin (Mutamycin)
Mitotane, o, p'DDD (Lysodren)
Procarbazine (Natulan)
Thioguanine (Lanvis)
ThioTEPA
Vinblastine Sulphate (Velbe)
Vincristine Sulphate (Oncovin)

HORMONES and SUBSTITUTES

Corticosteroids:
Cortisone (Cortisone, Cortone)
Fludrocortisone (Florinef)
Hydrocortisone (Cortef, Hydrocortone)

Androgens:
Fluoxymesterone (Halotestin, Oratestin)
Methyltestosterone (Metandren)
Testosterone Cypionate (Depo-Testosterone)
Testosterone Enanthate (Delatestryl)

Anti-estrogen:
Tamoxifen (Nolvadex)

Estrogens:
Chlorotrianisene (Tace)
Ethinyl Estradiol (Estinyl)
Stilboestrol
Stilboestrol Diphosphate (Honvol)

Progestogens:
Hydroxyprogesterone (Delalutin)
Medroxyprogesterone (Provera, Depo-Provera)
Megestrol Acetate (Megace)
Norethindrone

Thyroids:
Levothyroxine (Eltroxin, Synthroid)
Liothyronine (Cytomel, Tertroxin, Triiodothyronine)

AGENTS FOR THE TREATMENT OF DIABETES INSIPIDUS

Chlorpropamide (Chloramide, Novopropamide, Apo-Chlorpropamide, Stabinol, Diabinese, Chloronase)
Desmopressin (DDAVP, Minirin)

UNCLASSIFIED AGENTS

Allopurinol (Zyloprim, Purinol)

April 1983

HAMILTON

Director,
Ontario Cancer Foundation Hamilton Clinic
711 Concession Street
HAMILTON, Ontario L8V 1C3
(416) 387-9495

KINGSTON

Director,
Ontario Cancer Foundation Kingston Clinic
King Street West
KINGSTON, Ontario K7L 2V7
(613) 544-2630

LONDON

Director,
Ontario Cancer Foundation London Clinic
391 South Street
LONDON, Ontario N6A 4G5
(519) 679-9890

OTTAWA

Director,
Ontario Cancer Foundation Ottawa Clinic
190 Melrose Avenue
OTTAWA, Ontario K1Y 4K7
(613) 725-6300

THUNDER BAY

Director,
Ontario Cancer Foundation Thunder Bay Clinic
290 Munro Street
THUNDER BAY, Ontario P7A 7T1
(807) 345-1425

TORONTO

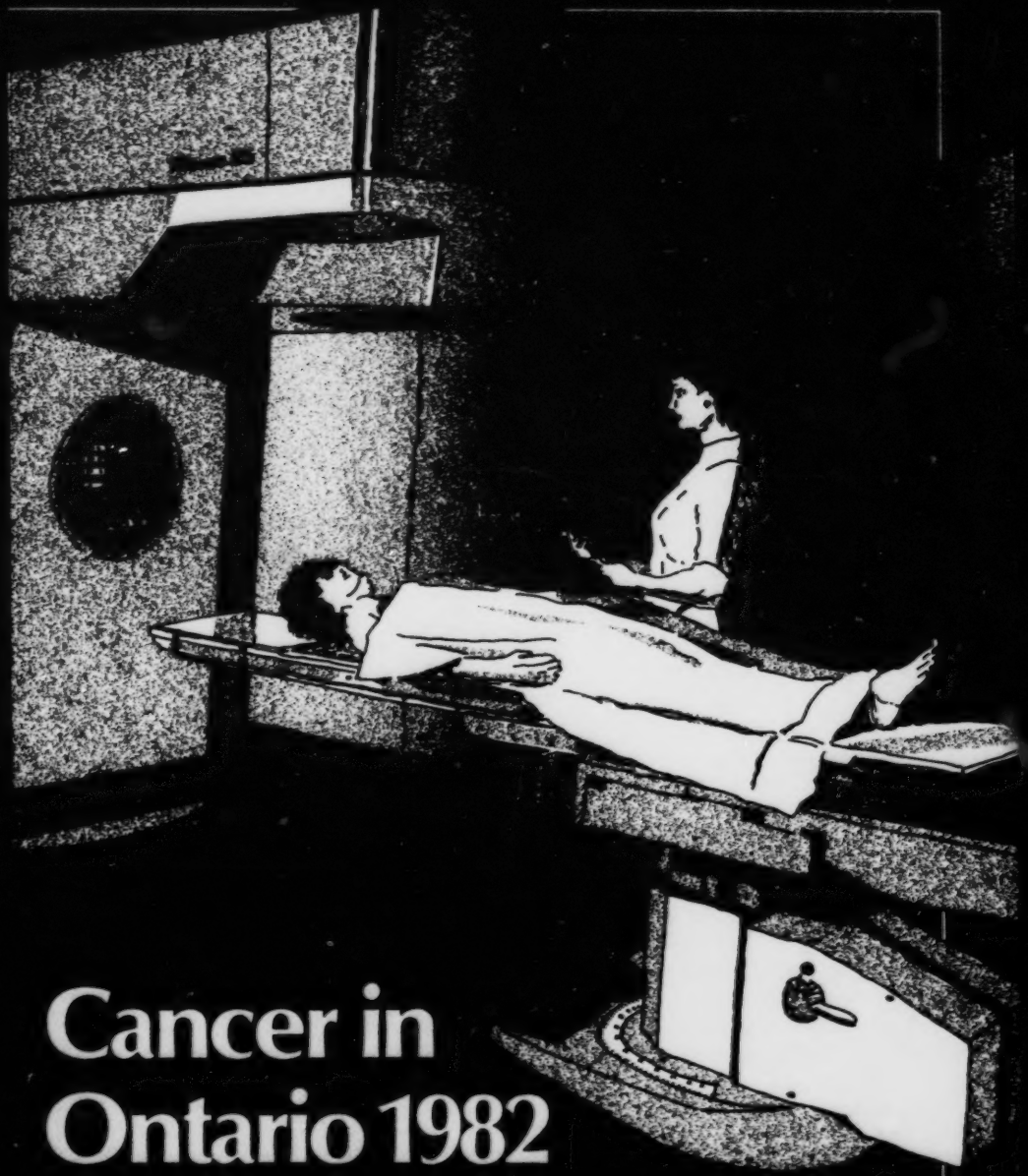
Director,
Princess Margaret Hospital
500 Sherbourne Street
TORONTO, Ontario M4X 1K9
(416) 924-0671

or

Director,
Ontario Cancer Foundation Toronto-Bayview Clinic
2075 Bayview Avenue
TORONTO, Ontario M4N 3M5
(416) 488-5801

WINDSOR

Director,
Ontario Cancer Foundation Windsor Clinic
2220 Kildare Road
WINDSOR, Ontario N8W 2X3
(519) 253-5253



Cancer in Ontario 1982

The Ontario Cancer Treatment and Research Foundation

The Ontario Cancer Treatment and Research Foundation was incorporated in 1943 by an Act of the Legislature of the Province of Ontario and reconstituted by The Cancer Act, 1957. The Cancer Act states that, "The object of the Foundation is to establish and conduct a program of research, diagnosis and treatment in cancer, including,

(a) the establishment, maintenance and operation of research, diagnostic and treatment centres in general hospitals or elsewhere;

(b) the transportation of patient and escorts to its treatment centres or to the hospital of the Institute for diagnosis, treatment or investigation;

(c) the establishment, maintenance and operation of hostels in connection with its treatment centres or the hospital of the Institute;

(d) the laboratory and clinical investigation of cancer problems;

(e) the co-ordination of facilities for treatment;

(f) the adequate reporting of cases and the recording and compilation of data;

(g) the education of the public in the importance of early recognition and treatment;

(h) the providing of facilities for undergraduate and postgraduate study;

(i) the training of technical personnel; and

(j) the providing and awarding of research fellowships."

Part II of The Cancer Act, dealing with The Ontario Cancer Institute, as amended by The Cancer Amendment Act, 1968-69, provides that the Institute Board shall consist of 15 persons appointed by the Lieutenant Governor in Council. Five members of the Institute Board shall be representatives of the Foundation, one of whom shall be the chairman of the Foundation. The Act specifies that one of the Foundation representatives on the Board of the Institute shall be the chairman of the Institute.

CANCER IN ONTARIO

1982

The Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard
Toronto, Ontario, Canada
M4H 1A8

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MESSAGE FROM THE NEW CHAIRMAN

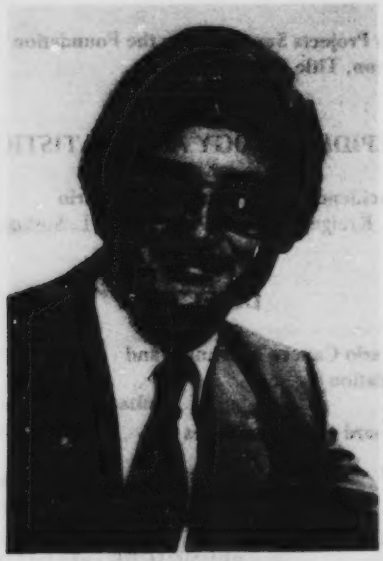


Photo: Tony V. Hauser

Michael A. Meighen, Q.C.

It was with great anticipation that I assumed the Chairmanship of the Foundation on July 15, 1982. The position of Chairman presents real challenges, particularly in the present economic climate. In spite of current fiscal constraints, the Foundation intends to move ahead with a number of vital projects.

Priorities for the coming year include the maintenance of high-quality treatment, education and research, and the improvement of cancer service in northeastern Ontario. Specifically, we will be undertaking the immediate expansion of the chemotherapy program sited at The Laurentian Hospital, Sudbury and the planning for establishment of a full cancer treatment centre with related programs. In addition we will launch a thorough re-examination of our provincial role in the delivery of oncological services, and the updating and computerization of the Ontario Cancer Registry.

I look forward to working with all of you to develop imaginative approaches to new problems and, with your co-operation, we will continue to work for the greater benefit for cancer patients throughout Ontario.

My best wishes to you all for 1983.

EXECUTIVE DIRECTOR REPORTS

1982 has been a "watershed" year. First, it marks the end of the first 40 years since passage of The Cancer Act, the mandate under which we operate. Second, the current recession is forcing the Foundation to examine its priorities closely in order to exercise this mandate effectively. The treatment of cancer patients remains our principal concern but if we are to treat at the forefront of knowledge, we will require ongoing and vigorous programs of education and research.

Diagnosis and Treatment

In 1981, 69,400 patients were seen at the Foundation clinics and the Princess Margaret Hospital – an increase of 3641 (5.5%) over the previous year. Malignant lesions accounted for 63,519 (91.5%) and, of these, 16,848 (26.5%) were new to the centres. During the year, patients made 396,201 visits to Foundation facilities, of which 19,250 were to the 28 peripheral clinics. Almost one-half (48.0%) of the visits by cancer patients were for treatment with radiation – most of these treatments (78.0%) were given to outpatients; Tables I-VI give more detail concerning the patient load.

The Foundation has made a number of advances in the treatment area. It has acquired new 6 MeV (six million electron volt) linear accelerators for radiotherapy for London and Toronto-Bayview Clinics and, the first commercially produced 25 MeV accelerator – Therac 25 – has just arrived in the latter clinic. A bunker has been constructed to house the London accelerator. Seven after-loading devices have been acquired to treat cancer of the uterus, in order to decrease radiation exposure to staff. Similarily, measures have been taken to provide a protective environment for staff preparing cytotoxic anticancer drugs. For further detail please see the sections on Epidemiology and Statistics, Special Services, and reports of the Regional Treatment Centres.

Education

During 1982, several new developments took place in our education program. The first H.E. Johns summer studentships, graduate and post-doctoral fellowships in medical physics were awarded to interest students of physics and allied disciplines in careers with medical applications. Second, the Royal College of Physicians and Surgeons of Canada has recognized the subspecialty of medical oncology – a measure the Foundation has long advocated. Third, the medical schools, recognizing the shortage of specialists in radiation oncology, have allocated additional resident

TABLE I

Malignant Caseload During 1981[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	1,146	87	207	89	795	2,324
Kingston	523	36	45	39	306	949
London	1,101	68	114	232	682	2,197
Ottawa	713	187	364	109	836	2,209
Thunder Bay	158	52	45	1	189	445
Toronto-Bayview	—	—	96	40	487	623
Toronto, PMH	3,611	1,260	823	278	1,230	7,202
Windsor	296	80	162	36	325	899
TOTAL	7,548	1,770	1,856	824	4,850	16,848
	Cases Registered in a Previous Year					
Hamilton	428	195	604	54	4,224	5,505
Kingston	184	34	81	35	2,213	2,547
London	292	113	301	224	6,300	7,230
Ottawa	257	208	739	115	5,070	6,391
Thunder Bay	70	31	92	1	861	1,055
Toronto-Bayview	—	—	123	7	162	292
Toronto, PMH	740	880	1,970	590	17,030	21,210
Windsor	58	56	408	31	1,888	2,441
TOTAL	2,029	1,517	4,318	1,057	37,748	46,671
TOTAL ALL MALIGNANT	9,577	3,287	6,174	1,881	42,598	63,519

[1] Includes cases seen at peripheral clinics.

TABLE II

Other (Non-Malignant) Caseload During 1981[1]

TREATMENT CENTRE	TREATED				SEEN FOR CONSULTATION OR FOLLOW-UP	TOTAL
	Radiation	Radiation and Chemotherapy	Chemotherapy and/or Immunotherapy	Other		
	Cases New in Current Year					
Hamilton	53	–	25	96	297	471
Kingston	11	–	–	45	157	213
London	108	–	1	440	496	1,045
Ottawa	6	–	–	6	65	77
Thunder Bay	4	–	1	–	76	81
Toronto-Bayview	–	–	1	78	110	189
Toronto, PMH	145	19	10	96	408	678
Windsor	21	–	3	6	131	161
TOTAL	348	19	41	767	1,740	2,915
	Cases Registered in a Previous Year					
Hamilton	4	–	5	2	137	148
Kingston	7	–	–	13	175	195
London	6	–	1	12	687	708
Ottawa	1	–	1	1	76	79
Thunder Bay	–	–	1	–	30	31
Toronto-Bayview	–	–	–	5	3	8
Toronto, PMH	30	10	120	40	1,466	1,666
Windsor	3	–	11	3	114	131
TOTAL	51	10	141	76	2,688	2,966
TOTAL OTHER	399	29	182	843	4,428	5,881

[1] Includes cases seen at peripheral clinics.

TABLE III

Cases Treated During 1981 by Method of Radiotherapy

METHOD OF TREATMENT	HAMILTON	KINGSTON	LONDON	OTTAWA	THUNDER BAY	TORONTO		WINDSOR	TOTAL
						BAYVIEW	PMH		
Malignant Neoplasms									
Superficial x-ray	400	203	129	33	29	–	418	–	1,212
Deep x-ray	128	20	–	–	9	–	687	155	999
Cobalt[60]	1,091	345	580	871	269	–	6,541	392	10,089
Cesium[137]	–	–	–	–	–	–	58	–	58
Betatron	–	–	408	–	–	–	413	–	821
Linear accelerator	433	307	725	611	–	–	1,178	–	3,254
Intracavitary	70	30	123	54	21	–	272	31	601
Interstitial	–	13	21	2	–	–	45	–	81
Moulds and applicators	–	–	4	–	–	–	–	–	4
Systemic isotopes	–	–	–	1	–	–	24	–	25
Others	–	–	–	–	3	–	–	–	3
SUB-TOTAL	2,122	918	1,990	1,572	331	–	9,636	578	17,147
METHOD OF TREATMENT	**Other Non-Malignant**								
Superficial x-ray	61	6	75	2	9	–	19	–	172
Deep x-ray	–	–	–	–	–	–	22	20	42
Cobalt[60]	8	10	19	3	–	–	53	8	101
Cesium[137]	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	23	–	23
Linear accelerator	4	1	19	3	–	–	26	–	53
Intracavitary	–	–	1	–	–	–	–	–	1
Interstitial	–	4	–	–	–	–	–	–	4
Moulds and applicators	–	–	8	–	–	–	73	–	81
Systemic isotopes	–	–	–	–	–	–	1	–	1
Others	–	–	–	–	–	–	–	–	–
SUB-TOTAL	73	21	122	8	9	–	217	28	478
TOTAL[1]	2,195	939	2,112	1,580	340	–	9,853	606	17,625

[1] A case can be treated by more than one method per year.

TABLE IV

Service Load, 1981

TREATMENT CENTRE	VISITS FOR					TOTAL VISITS
	Treatment				Consultation or Follow-Up	
	Radiation	Chemotherapy Immunotherapy	Other	Sub-Total		
	Visits for Malignant Neoplasms					
Hamilton	25,143	6,652	123	31,918	14,868	46,786
Kingston	11,995	699	54	12,747	8,162	20,910
London	24,598	2,412	585	27,595	20,987	48,582
Ottawa	23,018	10,964	597	34,579	31,711	66,290
Thunder Bay	5,308	1,390	5	6,703	4,375	11,078
Toronto-Bayview	–	1,509	36	1,545	2,859	4,404
Toronto, PMH	82,984	13,530	100	96,614	62,910	159,524
Windsor	10,565	5,939	76	16,580	8,280	24,860
TOTAL	183,611	43,095	1,576	228,281	154,152	382,434
TREATMENT CENTRE	Other Non-Malignant					
Hamilton	166	36	128	330	891	1,221
Kingston	98	0	82	180	684	864
London	548	22	592	1,162	3,135	4,297
Ottawa	136	13	8	157	377	534
Thunder Bay	30	15	–	45	265	310
Toronto-Bayview	–	3	96	99	177	276
Toronto, PMH	1,636	230	50	1,916	3,562	5,478
Windsor	272	55	11	338	449	787
TOTAL	2,886	374	967	4,227	9,540	13,767
TOTAL ALL VISITS	186,497	43,469	2,543	232,508	163,692	396,201

TABLE V

Treatments by Radiation During 1981, In-Patients and Out-Patients

METHOD OF TREATMENT	HAMILTON		KINGSTON		LONDON		OTTAWA		THUNDER BAY		TORONTO				WINDSOR		TOTAL	
											BAYVIEW		PMH					
	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out	In	Out
	Malignant Neoplasms																	
Superficial x-ray	–	1,855	25	843	8	522	–	165	–	148	–	–	54	1,618	–	–	87	5,151
Deep x-ray	94	593	34	66	–	–	–	–	1	55	–	15	516	2,437	20	2,139	665	5,305
Cobalt[60]	2,169	12,178	1,530	3,649	2,051	6,617	3,012	10,425	696	4,371	–	–	15,569	40,534	1,436	6,906	26,463	84,680
Cesium[137]	–	–	–	–	–	–	–	–	–	–	–	–	16	321	–	–	16	321
Betatron	–	–	–	–	931	4,006	–	–	–	–	–	–	819	5,636	–	–	1,750	9,642
Linear accelerator	1,289	6,875	722	5,078	3,342	6,953	2,146	7,190	–	–	–	–	3,172	11,947	–	–	10,671	38,043
Intracavitary	90	–	34	–	137	4	76	1	34	–	–	–	276	–	39	25	686	30
Interstitial	–	–	10	4	9	14	2	–	–	–	–	–	45	–	–	–	66	18
Moulds and applicators	–	–	–	–	–	4	–	–	–	–	–	–	–	–	–	–	–	4
Systemic isotopes	–	–	–	–	–	–	–	1	–	–	–	–	22	2	–	–	22	3
Others	–	–	–	–	–	–	–	–	3	–	–	–	–	–	–	–	3	–
TOTAL	3,642	21,501	2,355	9,640	6,478	18,120	5,236	17,782	734	4,574	–	15	20,489	62,495	1,495	9,070	40,429	143,197
METHOD OF TREATMENT	Other Non-Malignant																	
Superficial x-ray	–	80	–	19	–	77	–	8	–	30	–	–	2	36	–	–	2	250
Deep x-ray	–	–	–	–	–	–	–	–	–	–	–	–	22	86	–	92	22	178
Cobalt[60]	3	31	20	29	55	30	2	56	–	–	–	–	69	357	10	170	159	673
Cesium[137]	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Betatron	–	–	–	–	–	–	–	–	–	–	–	–	54	432	–	–	54	432
Linear accelerator	–	52	–	25	66	288	32	38	–	–	–	–	86	378	–	–	184	781
Intracavitary	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	–	–	1
Interstitial	–	–	3	2	–	–	–	–	–	–	–	–	–	–	–	–	3	2
Moulds and applicators	–	–	–	–	–	31	–	–	–	–	–	–	–	113	–	–	–	144
Systemic isotopes	–	–	–	–	–	–	–	–	–	–	–	–	–	1	–	–	–	1
Others	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
TOTAL	3	163	23	75	121	427	34	102	–	30	–	–	233	1,403	10	262	424	2,462
TOTAL OF ALL TREATMENTS	3,645	21,664	2,378	9,715	6,599	18,547	5,270	17,884	734	4,604	–	15	20,722	63,898	1,505	9,332	40,853	145,659

TABLE VI

Services at Consultative and Follow-Up Clinics[1], 1981

CLINIC	NEW CASES SEEN	VISITS
HAMILTON CENTRE		
Brantford	31	327
Guelph	12	275
McMaster	69	711
St. Catherines	10	304
Welland	34	290
TOTAL	156	1,907
KINGSTON CENTRE		
Cornwall, General	6	77
Cornwall, Hotel Dieu	5	101
Trenton	12	83
TOTAL	23	261
LONDON CENTRE		
Cambridge (Galt)	80	690
Chatham	143	1,155
Kitchener-Waterloo	189	1,237
Owen Sound	48	480
Sarnia, General	100	706
Sarnia, St. Joseph's	77	642
Stratford	141	788
Wingham	51	769
Woodstock	123	749
TOTAL	952	7,216
OTTAWA CENTRE		
Cornwall, General	64	541
Cornwall, Hotel Dieu	39	294
Pembroke, Civic	70	815
TOTAL	173	1,650
THUNDER BAY CENTRE		
Geraldton	1	60
TOTAL	1	60
TORONTO CENTRE		
North Bay	133	1,377
Owen Sound	82	809
Peterborough	117	1,843
Sault Ste. Marie	48	771
Sudbury	36	1,301
Timmins (South Porcupine)	44	965
TOTAL	460	7,066
WINDSOR CENTRE		
Leamington	40	1,090
TOTAL	40	1,090
GRAND TOTAL	1,805	19,250

[1] This table presents counts of new cases *first* seen *at* each Consultative and Follow-up Clinic and the number of patient-visits provided *at* these Clinics. It does *not* reflect the total cases from each of these areas nor the total services provided thereto.

positions to this field. The Foundation's 22nd biennial clinical conference was held in Kingston on October 19 on the subject of colorectal cancer; out-of-province lecturers were Dr. J. Decosse of the Memorial Sloan-Kettering Center, New York, and Dr. H. T. Enterline of the University of Pennsylvania School of Medicine, Philadelphia (see section on Education for further detail).

Research

In 1982, for the first year since 1945, the Foundation did not sponsor a competition for grant support. The dollars previously allocated for this purpose, with additional funds contributed by the Government of Ontario through the Terry Fox Fun (Ontario), are being used to increase the support of young scientists in our clinics and associated health sciences complexes to meet the competition from other jurisdictions, and to anticipate the retirement of many cancer researchers toward the end of this decade. Through the award of Provincial (lottery) funds, we have established an Ontario Clinical Oncology Group, based at the Hamilton Clinic and McMaster University, to carry out clinical trials aimed at improving our understanding, detection and treatment of cancer. In 1982, with the co-operation of the Cancer Research Co-ordinating Committee (the Foundation is a charter member), the Government of Canada became a supporting member of the International Agency for Research in Cancer (IARC) in Lyons, France; the Foundation has encouraged this link because of its working relationship with IARC in the field of cancer epidemiology. Further detail will be found in the section on Research Programs.

People

On July 15, 1982, Mr. Michael A. Meighen, Q.C. of Toronto was appointed Chairman of the Foundation. Mr. Meighen brings to the Foundation a rich experience in law, business, and public service including the health field. Mr. Gary Ross of Elliott Lake, who was appointed to the Board on February 19, 1982, also brings his experience in business to our affairs. Mr. W. A. Wilkinson received an honorary degree — Doctor of Laws — from the University of Windsor on June 5, 1982, in recognition of his outstanding public sevice.

Mrs. Henry C. Krug, O.C., of Kitchener retired from the Board after 13 years of exemplary service to the Foundation. She had also served the Canadian Cancer Society and her community devotedly. Her 80th birthday was recognized by the unusual honor of a Papal Blessing. Dr. F. L. Johnson of Hamilton and Mr. Alan B. Young of Burlington also retired from the Board after eight and six years of service respectively. To all we express our gratitude.

It is with great pleasure that we learned that Mr. G. R. Cunningham, former Member and Chairman of the Board, has been appointed a Member of the Order of Canada.

With great regret we record the death on April 3 of Mrs. C. J. S. Apps of Kingston. Mrs. Apps gave the Board 13 years of wise counsel.

Senior staff additions to the Foundation family include Mr. D. Horniachek, controller to the Head Office; Drs. N. Kreiger, C. Soskolne and L. Marrett (part-time), epidemiologists, to the Division of Epidemiology and Statistics; Dr. M. Levine, medical oncologist, and Dr. C. Kwok, physicist, to the Hamilton Clinic; Dr. G. Cairncross, neuro-medical oncologist, Drs. W. Kocha, L. Levin and J. Skillings, medical oncologists, to the London Clinic; Dr. D. Perrault, medical oncologist, to the Ottawa Clinic; Drs. I. Kerr and J. J. Rusthoven, medical oncologists, and Drs. P. A. Catton and R. G. MacKenzie, radiation oncologists, to the Toronto-Bayview Clinic.

The publications, one measure of the accomplishment of the staff, are recorded in Appendix B.

In 1982 we recognized three significant staff retirements. Miss Helen Young, Head Office Manager, who was the second full-time employee of the Foundation, had served it faithfully since 1946 and retired in September 1981. Dr. W. A. Hargan, the first Director of the Thunder Bay Clinic had served since 1948; Dr. Hargan continues as an active consultant. Dr. T. A. Watson, who was Director of the London Clinic from 1963 to 1980, served as an active consultant to the end of 1982.

It is with regret that we record the death, on October 21, 1982, of Dr. T. G. Stoddart, the former and first Director of the Ottawa Clinic.

1983

In the coming year we will celebrate the completion of 40 years of service to cancer patients in a variety of ways, both in the individual regions and province-wide, but also we will continue to plan and implement improvements in existing programs. With the assistance of the Ministry of Health and in co-operation with the Ontario Cancer Institute, the Foundation will carry out a role study of the delivery of cancer care in this Province with the aim of improving this service and making it increasingly cost-effective. The Ontario Cancer Registry, a valuable resource for planning and research for government, industry and health-related institutions will be upgraded to provide timely information on cancer incidence, prevelance, and mortality. Concomitantly the regional treatment centres will be automated to improve service to patients. Planning is underway to improve cancer services to northeastern Ontario. Also in 1983 we hope to have available for doctors a guide to cancer services in the Province. We are contributing to a re-organization of health research in the Province and have helped to plan the exposition, Health Research Ontario, scheduled for March 1983 in the Ontario Science Centre. Difficult times can also be exciting times.

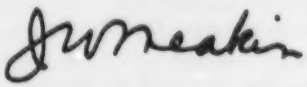
Finances

The programs of the Foundation are funded primarily by the Government of Ontario. However, in an era of recession, characterized by competition for available tax dollars, the Foundation must have financial support from other sources if it is to avoid a contraction in its programs.

One of its important supporters has been the Ontario Division of the Canadian Cancer Society who, both at regional and provincial levels, has provided some of the support for the construction and equipping of clinics and patient lodges and for special programs. The Society also maintains a close supporting liaison with the Foundation in providing special services to patients and professional education.

Legacies and donations continue to be of great importance in enabling the Foundation to maintain a reasonable program, especially in sustaining the level of its research activity over the past few years; even more support may be needed in the future. Appendix A of this publication contains a list of legacies and donations received and gratefully acknowledged.

May I conclude by thanking all who have contributed to the success of the Foundation and by soliciting your constructive comment for improved services in the future.



J. William Meakin, M.D., C.M., M.A., F.R.C.P.(C)
Executive Director

No annual financial statement is included in *Cancer in Ontario* but a copy of such statement will be provided upon request to the head office of the Foundation.

OBITUARIES

Mrs. C. J. S. (Molly) Apps
1915-1982

On April 3, 1982, Molly Apps died at her home in Kingston, at the age of 67. Molly was held in highest regard by all of her associates because of her warm friendliness, her keen appreciation of cancer problems and her willingness to apply her excellent judgment and energy to solve any problems facing her in her work on the Foundation Board and committees.

Mrs. Apps was appointed a member of the Foundation by Order-in-Council on April 17, 1969, and remained a member until her untimely death. She also served as Board representative on the Cancer Research Committee and as Foundation representative on the Joint Lodges Committee; the latter appointment gave her the opportunity to work with members of the Canadian Cancer Society in planning lodges for patients being treated as outpatients at the regional treatment centres.

Molly Apps graduated from McMaster University where she met her husband, Syl Apps who was an Olympic polevaulter, was long-time captain and centre of the Toronto Maple Leaf hockey team, and later for 11 years was a member of the Legislature for Kingston and the Islands and Minister of Correctional Services.

Mrs. Apps was active in a number of other organizations such as the IODE, the Red Cross, the United Way, the Helen Tufts Nursery School, the Kingston Historical Society, and the Kingston Library Board. She was a founding member of the Agincourt Baptist Church.

Molly Apps is survived by her husband, three daughters, two sons and 15 grandchildren. One of her sons, Syl Jr., was well known as a professional hockey player.

The Foundation extends its most sincere condolences to Mrs. Apps' family in their great loss.

Dr. T. G. Stoddart
1909-1982

On October 21, 1982, Dr. Thomas Glen Stoddart died in Ottawa in his 74th year. He graduated in 1934 from Queen's University, was Fellow of the Royal College of Physicians (Canada) and Fellow of the American College of Radiologists. A pioneer radiologist at the Ottawa Civic Hospital, Dr. Stoddart did both radiologic diagnosis and radiation therapy commencing in 1936. He was one of only three radiologists to serve the Ottawa area throughout World War II. Appointed Director of the Ontario Cancer Foundation Ottawa Clinic, Dr. Stoddart served in that role until November 1977, and concurrently headed the Department of Radiology at the Ottawa Civic Hospital.

In 1949, in response to the growing demand for radiological services in the areas surrounding Ottawa, Dr. Stoddart organized Radiological Associates — a partnership that continues to serve community hospitals. In 1962, Dr. Stoddart was appointed Professor of Clinical Radiology at the University of Ottawa.

Dr. Stoddart was best known as an oncologist, who treated cancer patients who came to Ottawa from Eastern Ontario and Western Quebec. The culmination of Dr. Stoddart's 25-year career as director of the Ottawa Clinic was the opening of the new Ottawa Cancer Clinic in April 1978. From 1966 to 1975 he was member of the Advisory Medical Board, the Executive Committee and the Committee on Cancer Centres. For four years after his retirement, he served in the Canadian Medical Protective Association and was an Honorary Consultant to the Ottawa Clinic. He was active in numerous charitable and professional associations.

He is survived by his wife, Marjorie, three children — Ian Glen, Linda Glen Shortt and Gail Marjorie Lalonde, and seven grandchildren, to whom the sincere sympathy of the Foundation is extended.

LANDMARKS IN CANCER RESEARCH IN ONTARIO

PIONEERING IN HODGKIN'S DISEASE

M. V. PETERS, O.C., M.D.*, *Oakville, Ontario*

As early as 1935 at the Toronto General Hospital, we were giving Hodgkin's patients high-dose radiation to massive disease sites. Because the radiation sources then available were of low intensity, special techniques were needed. Also we gave an added single low dose treatment to adjacent lymphatic regions in patients with higher radiation tolerances.

In March 1950, I reported an overall 5-year survival rate of 51% and 10-year survival rate of 35% in a series of 113 pathologically verified cases. This result was considerably better than any other reported survival rate. Analysis of these cases showed that the single most important influence bearing on the progress and ultimate survival of a patient with Hodgkin's disease was the extent of involvement at the institution of treatment. The second most important feature was the presence of constitutional symptoms on admission. Our work in Toronto demonstrated that the histopathological picture, which is the only proof of diagnosis, was of significant value in estimating the severity of the disease. In my experience, the younger patients responded to therapy better than the older ones. In women, Hodgkin's disease tended to run a more chronic course and hence they survived longer than did men.

This careful and detailed study, carried out more than 30 years ago, showed the critical points in the control of Hodgkin's disease to be:

- Early diagnosis and more optimistic attitude toward prognosis in early cases.
- Proper classification.
- Early institution of therapy.
- Moderately intensive treatment to the hopeful cases.
- Frequent follow-up.
- Institution of therapy to recurrences as early as possible.

This publication, which raised the probability of cure, was greeted with understandable scepticism. At that time my major support came from Rene Gilbert of Switzerland. A second paper, which I presented in Mexico City in 1956, aroused great interest. About this time, many cancer centres had begun reviewing their experience, and were finding that most of their cases had been treated too palliatively. By the early 1960's, eminent pathologists, immunologists, epidemiologists and therapists in all disciplines undertook what might be termed a "frenzy of studies".

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*Oncologist, Oakville, Ontario.

Working together, R. J. Lukes, pathologist to the DVA Hospital in Los Angeles and J. J. Butler, pathologist in the University of Texas Medical Center in Houston, discovered a previously unrecognized histological type in Hodgkin's disease — the nodular sclerosing lesion, which had a favorable prognosis. This histology nearly always was associated with mediastinal involvement. After this announcement (in February 1963 or 1964), Prof. Maurice Tubiana of Paris organized a unique symposium, which did much to dissipate the clouds of scepticism then prevailing. Prof. Tubiana invited all the major cancer centres throughout Europe, North America and Britain to send representative tissue slides on all their 10-year survivors and on an equal number of non-survivors. Three pathologists from these regions (Dr. Lukes representing North America), spent three weeks in Paris before the conference doing an independent review of all the slides. The diagnosis was verified unanimously in all but a very few cases. It was of great interest that 90% of the 10-year survivors had nodular sclerosing Hodgkin's disease. The report of this conference gave further stimulus to a better understanding of Hodgkin's disease. Prof. Tubiana's initiative in Paris marked an important turning point in the acceptance of Hodgkin's disease as potentially curable.

As the number of cases increased, I was able to define representative patterns of disease within each stage. This allowed the Princess Margaret Hospital group to individualize therapy and, by 1973, this institution had achieved much higher cure rates. Following this example, modern treatment planning now pays greater attention to patterns of disease. Chemotherapy was found to be more successful in the histological types other than nodular sclerosing disease. During the past 15 years, the addition of combination chemotherapy has doubled the cure rate, which in most centres has risen to almost 90%.

The advances achieved have been due largely to the work of therapists, whose efforts produced more successful treatment, more acute clinical assessment and more in-depth investigation. In time, international collaboration in clinical, immunological and epidemiological studies brought better understanding to the nature of Hodgkin's disease, giving new insight into its possible etiologies. This co-operation has brought agreement on histological and clinical staging classifications and has put disease assessment on a more secure foundation.

Editor's note: Our readers may be interested in a tribute paid to Dr. Peters by a distinguished British colleague, Sir David Smithers. In 1973, Sir David, reviewing the changes in Hodgkin's disease over a period of 40 years, said:

> *"Further improvement in the outlook for patients with Hodgkin's disease resulted from the work of Dr. Vera Peters in Toronto. She took over this interest from Dr. Gordon Richards, one of the outstanding pioneers in radiotherapy in the North American continent, a charming retiring man who concealed his shyness under a certain abruptness of manner. With his short, white moustache, bowler hat and trim, neat appearance, he had the air of a retired army officer. Building on the work Richards started, Dr. Vera Peters proceeded with system and sense to develop a planned radiotherapeutic attack on this disease process. This quiet and*

determined lady has written and spoken on the subject of Hodgkin's disease with clarity and persistence for a number of years. She showed us the importance to prognosis both of the anatomical extent of the disease and of its constitutional symptoms; she established a clinical staging system, compared the results of local treatment and of treatment extended to adjacent lymph-node regions apparently uninvolved, and showed how the addition of chemotherapy could affect survival. Modern staging and treatment of Hodgkin's disease are based on the foundations laid by Vera Peters. Through her, the approach of the medical profession to the disease was changed in two important respects: a staging system secured a better comparison of the results of treatment, and a more helpful outlook was encouraged among her comtemporaries." (*British Journal of Radio ogy* 1973; **43:** 911.)

THE COBALT-60 STORY

H. E. JOHNS, O.C., Ph.D.*, *Toronto, Ontario and*
T. A. WATSON, M.B., Ch.B.**, *London, Ontario*

For 30 years Canada has been a leader in the development of cobalt units for radiotherapy and in the application of basic physics to the use of high energy x-ray beams in the treatment of deep-seated tumors. Parallel political developments in the creation of centralized treatment centres and the efforts of Canadian radiation oncologists has produced across Canada therapy centres second to none. If one has to develop a deep-seated tumor one may be thankful to be a Canadian.

Canada was the first country to conceive of cobalt-60 as a radiation source for cancer treatment. For many years Canada had the only high-flux nuclear reactor capable of producing radioactive sources for therapy units. Today some 30 cobalt units are still in operation in Canada and it has been estimated that, in the whole world, outside the USSR and China, there are some 1500 units in operation. At the time when nuclear energy has come under attack it is worthwhile to review the cobalt-60 story and to appreciate what this device has done for medicine.

Between 1940 and 1945 a group of nuclear scientists were working secretly in Montreal and later in Chalk River on the design of a reactor, which could produce fissionable materials for the military and at the same time make many new isotopes available for medical research. During this period Prof. W.V. Mayneord from the Royal Cancer Hospital, London, England, worked with Dr. A.J. Cipriani of Atomic Energy of Canada Limited (AECL) in Chalk River studying the many new isotopes, which would suddenly become available through a successful nuclear reactor. These two men carried out an extensive survey of possible isotopes and "fingered" cobalt-60, which could be made from stable cobalt-59 by the addition of 1 neutron. Cobalt-60 decays with a half life of 5.2 years emitting two penetrating gamma rays of energy 1.17 million electron volts (MeV) and 1.31 MeV. The cross-section for the production of cobalt-60 is large so that intense sources of cobalt-60 could be made in a few months in a high-flux nuclear reactor. The half life for the decay of cobalt-60 is long enough to make a practical therapy unit.

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*Former Head of Physics Division, Ontario Cancer Institute, Toronto; and Consultant to the Ontario Cancer Treatment and Research Foundation.

**Former Director, Ontario Cancer Foundation London Clinic.

Editor's Note: Drs. Johns and Watson worked together in Saskatchewan during the early development of high energy sources for radiation. Both Dr. Watson and Dr. Johns continued their developmental work on coming to Ontario.

In 1946, at the invitation of Dr. Gordon Richards, Prof. Mayneord delivered a course of lectures at Toronto General Hospital on the physics of radiotherapy. I attended these lectures and was asked to prepare a set of notes[1], which later became the first draft of a textbook titled "The Physics of Radiology", now in its 4th edition[2]. This textbook has been translated into Spanish, Russian and Chinese. Prof. Mayneord spoke with great excitement about the possibilities of cobalt-60 as the source of radiation in a therapy unit and of the use of a 25 MeV beam from a betatron for radiotherapy. The betatron, developed initially to radiograph steel castings of battleships, was being investigated at the University of Illinois at Urbana under the leadership of Prof. Kerst. Mayneord and Kerst could see the potential in cancer therapy of both high-energy electrons and x-rays from the betatron. (This review must include happenings with betatrons as well as cobalt-60 units because the two complemented each other).

Dr. Cipriani, in Chalk River, created thin wafers of cobalt-59 in readiness for the completion of Canada's high-flux nuclear reactor. These wafers were activated between 1948 and 1950. Three sources were produced in the reactor[3]; one for Prof. Mayneord, one for Dr. Ivan Smith at the Ontario Cancer Foundation London Clinic, and one for us at University Hospital, Saskatoon. In the end Prof. Mayneord declined his source and it was sent to Dr. Gilbert Fletcher at the M.D. Anderson Hospital in Houston, Texas.

In the period 1946-1950, a group at AECL including Green and Errington[4] designed and built units to hold a source. The basic measurements on the beam from this unit were performed by Morrison, Garrett and Dixon[5] at the National Research Council (NRC) in Ottawa and then the unit was shipped to Dr. Smith in London. This unit, called the Eldorado unit, was supported on a vertical column and could be raised or lowered or angled on any direction. This unit used an ingenious shutter, which allowed the operator to force mercury into the space between the source and the patient to turn the machine "off". To turn the machine "on", the mercury was pumped from this space into a reservoir. The width and length of the rectangular beam from the machine could be selected by an ingenious collimator consisting of four heavy metal bars coupled together and moving in one plane.

At the same time, working with John MacKay of the Acme Machine Electric Co., Saskatoon, we designed and built our version of a cobalt-60 unit[6,7]. The Saskatoon unit was mounted on an overhead carriage, which moved along the ceiling. This unit could be translated, rotated and raised or lowered allowing for maximum flexibility in directing the beam at a patient. The radioactive source was mounted on a wheel, which could be turned through 180 degrees to turn the beam "on" or "off". In this unit the beam size was first defined by a set of interchangeable cones, which were shortly replaced by a cunning new design called the multivaned collimator[8]. Cobalt-60 units being made today still combine some aspects of these early designs.

It is hard to envisage 30 years later the bold steps, which were taken in those days. The units had to be safe so that in any emergency the source was automatically returned to the "off" position. At the time we were designing the Saskatoon unit, we

tended to think of it as a large version of the teleradium units of those days. In these units the radium was stored in a lead safe and connected to the treatment head by a flexible metal hose so that, once the unit was positioned on the patient, the source could be drawn from the safe to the head with compressed air.

On visiting Manchester in 1950, I was present when the physicist was called to "unstick" their teleradium unit. He disconnected one end of the hose and prodded the source back into the safe with a long stick. This would be extremely dangerous with a cobalt-60 source because survival time 1 metre from such an unshielded source would only be a few minutes. The teleradium design was ruled out instantly as a possible design for cobalt-60.

The beam from the cobalt-60 unit, if properly collimated, consists of only high energy photons, which produce no dose on the superficial layers of the skin — the dose reaching a maximum at a depth of about 6 mm. This buildup is an important aspect of a cobalt-60 beam. This was realized in the Saskatoon unit but initially was not realized in the Eldorado unit. The latter used a plastic cone whose apex was pointed at the centre of the radiation field. Although this was an excellent beam director, it brought the high-dose beam directly onto the skin surface. Detailed studies on this problem were carried out in Saskatoon[9].

At that time we knew of no way to transport the cobalt-60 source from one place to another. The group in Saskatoon were prepared, if necessary, to haul the source from Ottawa to Saskatoon on a trailer. Fortunately, the railroads did this for us, with no unnecessary red tape.

As a result of phone calls to Miss Sylvia Fedoruk in Saskatoon and Miss Elaine Marshall in London, we have established the following dates for events related to the development of high-energy radiation in the treatment of cancer in Canada.

First patient treated on 25 MeV betatron in Saskatoon by Dr. T. A. Watson	March 29, 1949
Cobalt-60 source delivered to Saskatoon	July 30, 1951
Cobalt-60 source loaded into unit at Saskatoon by Dr. H.E. Johns and Mr. J.A. MacKay	August 18, 1951
Official opening of cobalt unit in Saskatoon by Dean Cronkite of the University of Saskatoon	October 23, 1951
First patient treated on cobalt-60 unit in London by Dr. Ivan Smith	October 27, 1951
First patient treated on cobalt-60 unit in Saskatoon by Dr. T.A. Watson	November 8, 1951
Official opening of cobalt-60 unit in London	November 11, 1951

The opening ceremonies for the Saskatoon cobalt-60 unit took place on Tuesday, October 23, 1951. Because of weather conditions none of the politicians could fly up from Regina for the ceremony. In any case Saskatoon did not show much interest in the cobalt-60 unit, because earlier, in March 1949, we had made a big step forward by installing and using a 25 MeV betatron for treatment.

In contrast, the opening ceremonies of the cobalt-60 unit in London, Ontario, on November 11, 1951, was a media event which was given full coverage in local and national news. The first patient was treated on a cobalt-60 unit in London, on Saturday, October 27, 1951. The patient was positioned under the beam by Dr. Ivan Smith and Elaine Marshall, and the unit was turned on by Dr. Smith. The first patient in Saskatoon was treated 12 days later. For many years friendly rivalry existed concerning who had the first unit. You be the judge. In any case, at this point, it does not matter. Of more importance is the question, What does this all mean?

The introduction of cobalt-60 in many centres across Canada and throughout the world heralded the high energy era of radiotherapy which, in a number of ways, constituted a major breakthrough in the fight against cancer.

In retrospect, one important result was the introduction of radiation physicists into every centre using the cobalt-60 unit. In Canada this happened because the Atomic Energy Control Board would not license a cobalt-60 unit for any centre without a physicist. The cobalt-60 unit produces no skin effect where the beam enters so the oncologist could not use the reddening of the skin to judge the extent of the treatment. Besides, the installation of each unit required careful physical measurements before the beam could be safely used.

Because cobalt-60 decays in a precise way, the dose rate from each field can be specified with precision into the future without any measurement. Thus, once created, a table of dose rates can be used for a long period by merely correcting the dose rate for the decay of the source at 1.1% per month. This built-in precision has profound effects on the comparison of doses in various parts of the world. The physicist has a difficult problem in dealing with dose meters calibrated by the Bureau of Standards in Washington or NRC in Ottawa. If a newly calibrated detector showed a different dose rate for a particular collimator setting of a cobalt unit from that predicted by the decay of the source, which value (if either) is correct? The physicist, the standardization lab or both could have made a mistake, or the dose meter could have been damaged in transit. Agonizing decisions over such inconsistencies took place all over the world and various centres were referred to as using "hot rads" rather than "cold rads". The point is that cobalt-60 made possible a standardization of dose from centre to centre, which never had been achieved before. In the era before cobalt-60, inconsistencies were covered by merely saying the output from the unit had changed!

Oncologists and physicists realized that a cobalt-60 unit was in every way equivalent to a 3 MeV x-ray machine but much simpler to operate. The unit can operate without problems in even an unsophisticated environment. Cobalt-60 units were thus a simple valuable source of radiation for developing countries.

Perhaps the most important aspect of cobalt-60 therapy was the improvement it produced in cure rate. In particular, cure rate of cancer of the cervix went from 25% to 75% with the introduction of high-energy machines, cobalt units and betatrons. Linear accelerators and betatrons, because of their better dose distribution, gradually are replacing cobalt-60 units but the cobalt-60 unit always will have a place in therapy departments because of the precision of its dose delivery.

In Saskatoon we once had a 400,000 volt x-ray machine in a room adjacent to a cobalt-60 unit. We realized suddenly that the cobalt-60 unit was about 1/10 as large, delivered radiation at 10 times the energy and at 10 times the rate. No wonder 400,000 volt machines became obsolete overnight. At the present time linear accelerators are being installed in many centres. The latest unit, made by AECL, uses a short wave guide because the electrons are accelerated down the wave guide once, turned around in a magnetic field to be further accelerated in the same wave guide as they travelled back. Using this "turn-around" principle, the Therac 25 unit operating at 25 MeV is not much bigger than a cobalt-60 unit and can deliver 10 times the dose rate, so a patient can be treated literally in a few seconds. Precise use of these new machines again will increase cure rate.

A major development of the '80s is the CT scanner. With it, the oncologist can see in a cross-section normal tissues, tumor tissues and the super imposition of radiation beams on these cross-sectional beams. Today every first-class radiotherapy centre needs the in-house capabilities of CT scanners to ensure that all of the tumors are correctly placed within the radiation beam. The collaboration of the physicist and the oncologist is more than ever required to meet the challenge of the '80s.

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THE BEGINNINGS OF VINCA ALKALOIDS

O. H. WARWICK, M.D., F.R.C.P.(C)*, *London, Ontario*

Twenty-five years have passed since reports first appeared in the literature on the subject of alkaloids found in the common periwinkle plant, *Vinca rosea L.* This essay reviews the first efforts to isolate a biologically active principle and determine its effects, if any, on human tumors. Opening a symposium on the vinca alkaloids at the Fourth Canadian Cancer Conference, Dr. Robert Noble had this to say concerning these beginnings and about the studies he conducted with Drs. C.T. Beer and J.H. Cutts at the Collip Laboratories of the University of Western Ontario: "In 1949 we were intrigued by various plant extracts to which historical hearsay had ascribed empirical cures by primitive peoples. Cancer was far from our minds when we learned from a Miss Farquharson of Toronto that during visits to Jamaica she had heard of the periwinkle plant (*Vinca rosea*) being used for the treatment of diabetes mellitus. We have never been able to demonstrate any effects of extracts of this plant on carbohydrate metabolism. However, when we injected extracts into rats, we noticed that frequently there was a fulminating infection with septicemia, and that during this time the circulating white blood cell count was depressed".

Interest then centred on determining what substance in the plant was affecting the white blood cell count and the bone marrow. Eventually an active principle was extracted as the sulfate and named vincaleukoblastine (VLB). In 1958, before a meeting of the New York Academy of Sciences, Dr. Noble described the assay and isolation of VLB and showed pictures of its crystalline form. He also reported that, as material had become available, his group had carried out limited investiagations to test its carcinostatic activity. They noted effects on mammary cancer in mice and on a transplantable sarcoma in rats.

In the audience at this meeting were Drs. I.S. Johnson and G.H. Svoboda of the Eli Lilly Company of Indianapolis. They also had been searching for an antidiabetic substance in the periwinkle plant and during routine screening against mouse leukemia, had found that one of their extracts had activity. Building on this common interest the two groups maintained close co-operation until the Eli Lilly Company was able to produce enough VLB for adequate clinical trials. It was an enormous undertaking, e.g. the company had to process 10 tons of periwinkle leaves in order to isolate one ounce of VLB. However, before they reached this point Dr. Beer, in his laboratories at

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the University of Western Ontario, had produced about 200 mg of crystalline VLB – enough to start clinical investigation. Part of this precious material was sent to Eli Lilly Company, but the largest part (approximately one-half) came to the Princess Margaret Hospital.

The initial clinical trials were conducted at three centres – the Ontario Cancer Institute incorporating the Princess Margaret Hospital in Toronto, the National Institutes of Health in Bethesda, Maryland, and the Indiana University Medical Center in Indianapolis. I knew Bob Noble very well through our association with the National Cancer Institute of Canada and was familiar with the developing story of the vinca alkaloids. On a spring morning in 1959, he and Dr. Beer appeared at the Princess Margaret Hospital with 10 vials each containing 10 mg of crystalline VLB prepared at the Collip Laboratories in London. Strict regulations governing the introduction of new medicinal agents did not then exist. We knew, however, that the dosage in animals and the biological effects had been well documented and hence, with informed consent, felt justified in giving VLB to patients with advanced disease, which had not responded or was no longer responding to established forms of treatment.

The Indiana group submitted their early experience with VLB in an abstract to the *Journal of Laboratory and Clinical Medicine* (Nov. 1959). The first detailed reports of clinical experience with the new agent were received for publication by *Cancer Research* in the early part of January 1960 and appeared in Vol. 20, 1960. The reports from Toronto and Indiana both noted beneficial effects in acute leukemia and the lymphomas. We commented on a significant drop in urinary gonadotrophins in a patient with chorioepithelioma and reported partial remission in cancer of the breast. Our first patient with Hodgkin's disease was very sick. Although lymph nodes and other masses became smaller after treatment, he developed severe gastrointestinal bleeding probably from a duodenal ulcer. We could not rule out the possibility of an adverse reaction to VLB and hence treatment was stopped. He was recorded as showing no improvement. The striking effects of VLB in Hodgkin's disease did not become clear until further experience was reported at the Canadian Cancer Conference in the summer of 1961. That meeting was attended by all of those from the United States who had been engaged in the initial studies, and all gave papers. By that time we had treated 46 patients of all types compared to the Indiana total of 55. Five of our six patients with Hodgkin's disease had responded to treatment and the Indiana group reported that all five of their patients had a good response.

Reports from the National Institutes of Health which related only to trophoblastic tumors, noted that five of eight patients who had become resistant to methotrexate achieved remission, and for the first time described peripheral neuropathy as a complication of repeated courses of VLB.

In September 1961 the Princess Margaret Hospital reported a two-year experience in 120 patients treated with VLB. By that time we concluded that, from the standpoints of dosage and schedule, we had learned how to use VLB without causing serious side effects. Furthermore, we had demonstrated that VLB produced useful remissions in

advanced Hodgkin's disease. We had favorable responses in 16 of 27 patients and remissions of up to 11 months duration – a significant achievement in those days.

Apart from Hodgkin's disease and choriocarcinoma, the introduction of VLB in the years 1959 to 1961 did not make any great contribution to the day-to-day management of other forms of cancer. On the other hand, these results encouraged scientists to search for other alkaloids from plants, and physicians soon began using combinations of the several classes of chemotherapeutic agents now available. VLB, it had been shown, represented a new class of agents. It interfered with mitosis by causing metaphase arrest. Shortly after the events described here, the Lilly laboratories isolated vincristine; the form, then available, contained only 1/100 VLB.

Of the two vinca alkaloids, vincristine was the agent of choice clinically for almost two decades but, in recent years, VLB has played an important role in the treatment of regimens for an expanding spectrum of tumors. Leurosine, a third alkaloid, was initially isolated by Svoboda but proved less stable and less active in brief clinical tests. Vindestine, synthesized from VLB by the Lilly group, promises to be effective in the management of acute lymphoblastic leukemia, breast cancer and malignant melanoma. In combination with other agents, the vinca alkaloids now are used with curative intent in acute leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, cancer of the testis and choriocarcinoma.

Any person with experience in cancer medicine is acutely aware of the limitations of chemotherapy, yet it is saving some lives and is helping many patients to live with their disease. Progress in this field continues and no one can predict with certainty where and when new advances will be made. The story of the beginnings of the vinca alkaloids is a classical example of the importance of chance observation in scientific discovery. It is also a heartening example of the importance of international scientific co-operation dedicated to a common end. Drs. Noble, Beer and Cutts have made a significant contribution to medical science. Their work is a milestone in the development of cancer chemotherapy and a milestone in Canada's continuing efforts in cancer research. Those of us at the Princess Margaret Hospital were privileged to be able to participate in the first clinical trials of this new and important chemotherapeutic agent.

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STEM CELLS IN HEMOPOIESIS AND MALIGNANCY*

In the late 19th century, when the microscope and special preparation methods were applied to the study of disease, blood cells were among the first objects to be examined. Noting that mature red cells, white cells and platelets could be traced to more primitive ancestors, early workers deduced that all blood cells might have a common ancestor — the hemopoietic (blood-forming) stem cell. The existence of this cell was hypothetical until two scientists at the Ontario Cancer Institute in Toronto did a novel experiment. They administered large doses of radiation to mice in order to destroy their blood-forming tissues and then injected each mouse with 10- to 100-thousand marrow cells from healthy donors. After 10 days the spleens of the irradiated recipients contained visible lumps, which could be counted easily. The lumps proved to be colonies, each derived from a single cell from the injected marrow. The cells within the colonies consisted of the three types of blood cells — red cells, white cells and platelets. Hence the cell of colony origin — the colony-forming unit (CFU) — was shown to be a hemopoietic stem cell. Counting spleen colonies became a widely accepted method for measuring stem-cell numbers, while analysis of the colonies disclosed many stem-cell properties. The spleen colony technique came to be known as the Till-McCulloch assay, after the two investigators who first described it. During the ensuing 20 years, the spleen colony method has been the "gold standard" for experimental studies of blood formation, and today remains in widespread use.

Moving the stem cell from hypothesis to experimental reality gave powerful impetus to the study of both normal and leukemic blood formation. The work became of greater importance when Fialkow and his colleagues showed that many leukemias begin in hemopoietic stem cells; it became obvious that these, not their descendants, were the correct targets for treatment. Also it soon became evident that "stem cell concepts" were not restricted to blood formation, rather it was observed that the cells of many cancers, perhaps all cancers, were organized like hemopoiesis. Continuing research showed that the cell populations in cancers were not uniform: only a few of them were capable of continuous growth, while the majority were able to divide a few times or not at all. The active minority had biological properties similar to those of hemopoietic stem cells, hence they came to be called tumor stem cells. As in leukemia, tumor stem cells, not all of the cells in a cancer, were perceived to be the targets for treatment with drugs or radiation. Generally speaking, these insights into cancer were built on the understanding of cell

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*Contributed through the courtesy of the Ontario Cancer Institute, Toronto.

growth and tissue organization achieved through the use of the Till-McCulloch method.

Till and McCulloch have been well recognized for their work. Their papers are often cited by other authors. In 1969, they shared a highly-prized international honor — the Gairdner Award. Both have been elected to the Royal Society of Canada and have received national and international recognition. Each has held important university and hospital appointments. Perhaps of even greater importance, Drs. James E. Till and Ernest A. McCulloch continue to be active and productive in cancer research.

THE MULTICELL SPHEROID — AN IN VITRO TUMOR MODEL

W. R. INCH, Ph.D.*, *London, Ontario* and
R. M. SUTHERLAND, Ph.D.**, *Rochester, N.Y.*

Multicell spheroids are composed of cancer cells growing in a three-dimensional structure simulating the growth and microenvironmental conditions of intervascular regions of real tumors or of micrometastatic disease. Spheroids can be used in a variety of research areas as an in vitro tumor model system of intermediate complexity between standard monolayer or suspension cultures and tumors in vivo.

Initiation and growth of multicell spheroids has been accomplished with many different types of tumor cells using suspension cultures in spinner flasks or growth of cells in liquid overlay cultures on non-adherent surfaces such as agar or special non-tissue culture plastic dishes. Initial formation of spheroids often involves aggregation of cells which then grow to a diameter of 1 mm or even larger (Fig. 1). Under appropriate conditions, hundreds of spheroids of any required size can be grown in flasks for experimental purposes. Concentration gradients of oxygen, nutrients, and other factors develop within spheroids as they increase in size. Necrotic centres often develop in spheroids greater than 400 μm diameter because of diffusion limitations, similar to the situation associated with abnormal vascularization of many tumors. Histologically, the organization of the viable rim of cells surrounding the necrotic centres differs significantly for different cell types. Different types of intercellular junctions occur in spheroids. Often the frequency and types of junctions seen are similar to those observed in solid tumors of the same histological type. Studies of cell growth kinetics have shown that the growth fraction decreases as the spheroids grow; the non-proliferating fraction of the cells is found in the central regions and proliferating cells, which synthesize DNA as measured by incorporation of radioactive thymidine, are located in the periphery (Fig. 2).

This heterogeneity of cells and microenvironments, which develop within spheroids, makes this model useful to study the characteristics of the cell subpopulations and the importance of environmental factors such as oxygenation. Direct measurements of oxygen concentration profiles within spheroids have been performed using microelectrodes. The degree of hypoxia in the central region varies with the cell type and may not be severe enough to produce radiation resistance in some experimental situations despite the presence of necrosis. This suggests that sometimes necrosis may result from a deficiency of nutrients other than oxygen, such as glucose. Differences in supply of both oxygen and glucose produce major effects on the growth, cell-cycle phase distribution, and clonogenicity of cells within spheroids.

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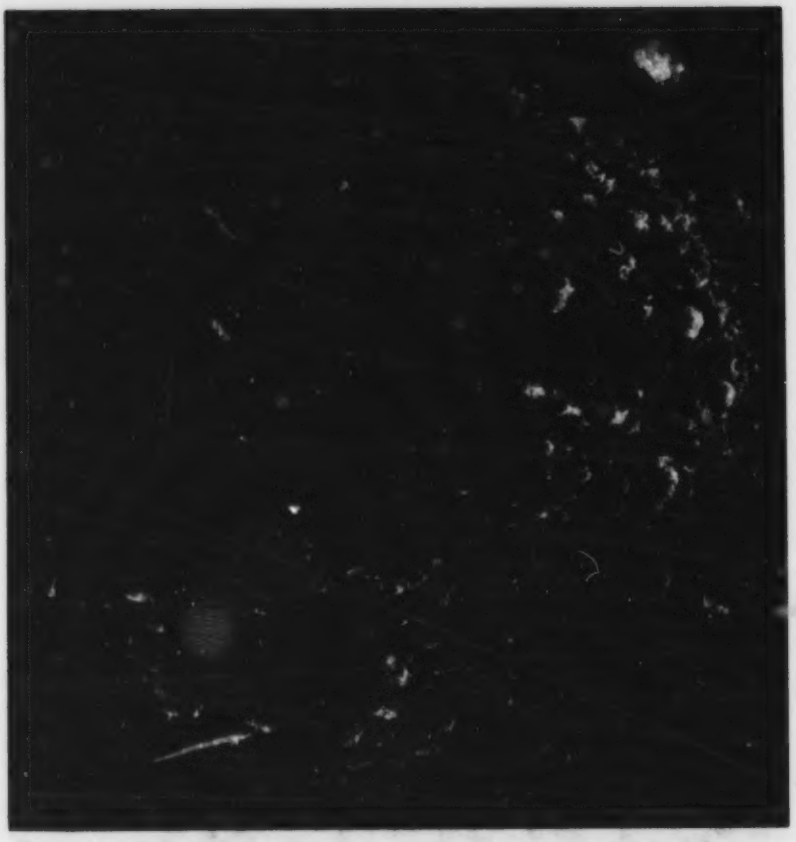

Fig. 1. Multicell spheroid of mouse EMT6 mammary tumor, approximately 550 μm diameter, 4 x 10^4 cells.

Sequential dissociation of spheroids with enzymes has been used to demonstrate changes in cells from different regions. Non-proliferating cells in the central regions differ in size and density and therefore can be isolated for further experimentation by centrifugation techniques.

In addition to this research on the basic biology of spheroids, this model system has been used by many research workers to investigate responses of cells in a tumor-like

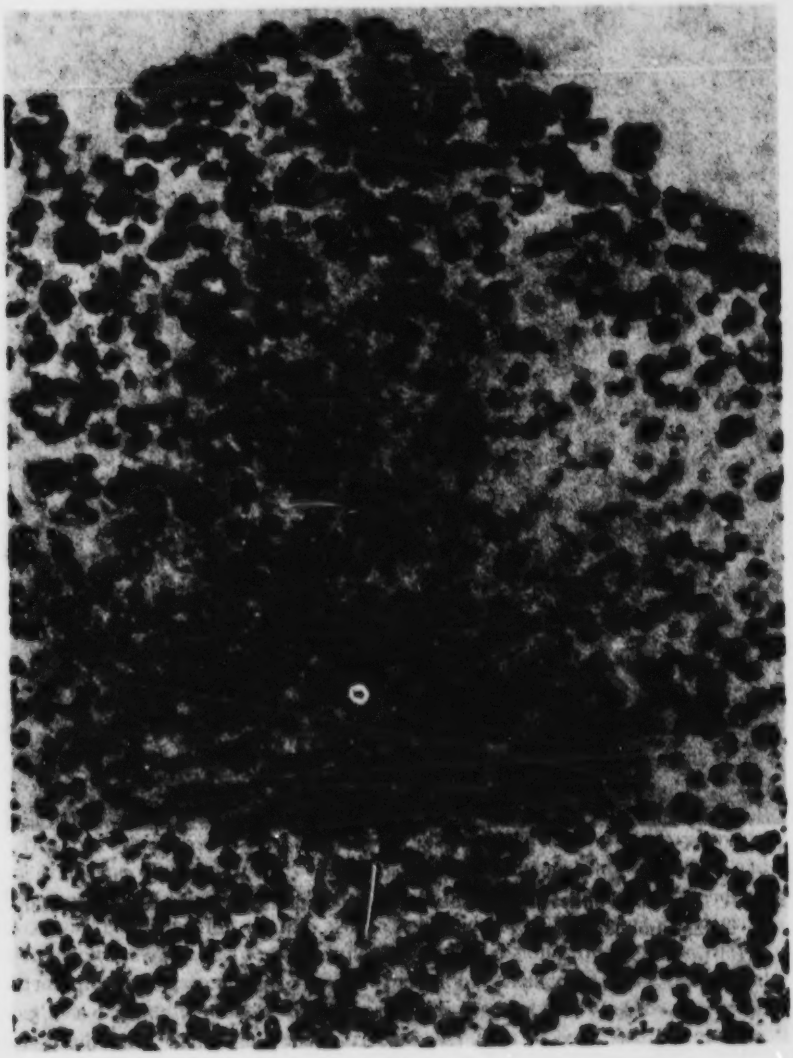

Fig. 2. Cross-section of V79 hamster lung spheroid. Autoradiograph showing ^{3}H-thymidine incorporated into peripheral cells. Note small necrotic centre.

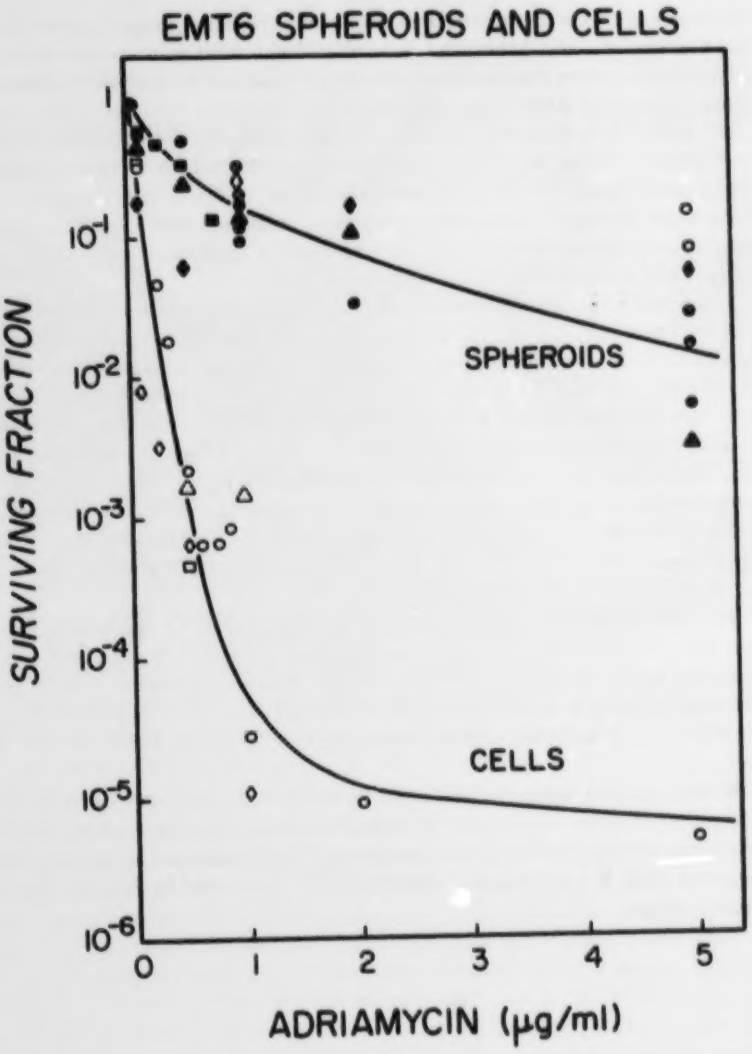

Fig. 3. Response to Adriamycin of EMT6 spheroids compared with monolayer cells.

structure to different therapeutic modalities such as radiation, drugs, hyperthermia, and host immune cells. Spheroids can be treated with these agents separately or in combination and then dissociated into a single cell suspension for analysis of sensitivity using a clonogenic assay. Quantitative dose response curves have shown that some small spheroids are more resistant when exposed (as spheroids) to radiation or heat than when treated as single cells. This resistance is reflected mainly by a change in the low-dose region of the dose-response curve indicating that an increased ability to accumulate damage is associated with growth condition, which facilitate close intercellular contact. Several types of larger spheroids contain cells which are hypoxic and, consequently, radiation resistant.

Spheroids also are useful for tests of the cytotoxicity of different drugs. Penetration barriers, which exist in poorly vascularized regions of tumors, can in part be simulated. Several workers have studied the primary sensitivities to different drugs and development of resistance associated with repeated exposures. Several nitroheterocyclic drugs have been evaluated for their ability to sensitize hypoxic cells to radiation. Also some of these drugs are preferentially toxic to hypoxic cells even without x-radiation, and have been demonstrated to act as chemosensitizers, that is, they sensitize tumors to some normal cancer chemotherapy agents. Resistance of non-proliferating hypoxic cells in spheroids can be visualized using drugs tagged with radionuclides or fluorescent chemicals combined with histology. This effect can be quantified with clonogenicity assays as was shown for Adriamycin (Fig. 3).

Multicell spheroids also can be used for immunologic studies, they can be implanted into the peritoneal cavity of normal or sensitized allogeneic or syngeneic mice, recovered at later times, and studied to determine host-cell infiltration, kinetics and functional properties, as well as the effect of this infiltration on tumor-cell viability. Modifications of tumor-host interactions by different therapy modalities also can be evaluated.

Research to date using this model system has demonstrated its usefulness as a supplement to other culture techniques and tumors in mice. There are significant differences among different types of cells grown as spheroids, just as there are real tumors in mice. We are now beginning to extend this method to direct studies of human tumors.

CLASSIFICATION OF MALIGNANT TUMORS: THE TNM SYSTEM

A. H. SELLERS, B.A., M.D.*, *Toronto, Ontario*

The search for basic principles to guide the classification of cancer cases by anatomical extent of disease has been pursued for almost a century but has achieved little uniformity. Such a classification is recognized as a valuable clinical tool, but despite many significant contributions, except for cancer of the cervix, the progress toward international agreement had been quite limited until 1953. The principal purpose to be served by international agreement on a system of classification of cancer cases is to provide us with a method of communicating our experience to each other without ambiguity. To gain wide acceptance and use, such a system of classification must be simple, practical and sensible.

The clinician's immediate task is to make a judgement as to prognosis and a decision as to the most effective course of treatment. This judgement and this decision require, inter alia, an objective assessment of the anatomical extent of the disease. In accomplishing this, the trend is away from "staging" to meaningful description, with or without some form of summarization.

To meet the stated objectives we require a system of classification:

- whose basic principles are applicable to all sites regardless of treatment;
- which is based on detailed description of the anatomical extent of disease before treatment (TNM); and
- which may be supplemented by information which becomes available later from surgical operation and histopathology (p.TNM).

The TNM system meets these requirements.

The philosophy and technique of the TNM system of clinical stage classification were developed by Prof. P.F. Denoix at the Institute Gustave-Roussy during the years 1943 to 1952. Denoix presented the TNM system to the International Commission on Stage-Grouping of Cancer and Presentation of Results (ICPR) of the International Congress of Radiology at its first meeting in Copenhagen in July 1943. The system was accepted by the ICPR as the basis for its classification proposals for breast and larynx. Following this acceptance, the UICC in 1954 established an internationally representative Committee on Clinical Stage Classification and Applied Statistics to extend to general TNM technique to cancer of other sites. Prof. Pierre Denoix served

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as chairman of the committee until 1966 when Mr. Michael Harmer (U.K.) succeeded him; the committee was then renamed the Committee on TNM Classification. Prof. B. Van der Werf-Messing of Rotterdam became Chairman in 1974 and Dr. Leslie Sobin (USA) in 1982.

The TNM system emphasizes clear-cut description of anatomical extent rather than "stage-grouping"; it offers clinicians a convenient, descriptive, international language.

The TNM system began as a purely clinical system for the description and classification of malignant tumors by anatomical extent of disease, based on clinical examination, radiography and endoscopy. This was widely accepted for the accessible sites but presented many difficulties for the inaccessible ones.

At the meeting of the UICC Committee on TNM Classification in Geneva in September 1976, the difficulties posed by inaccessible sites were thoroughly discussed and it was decided to adopt a "two-level" classification, separated by a point in time – the decision as to definitive treatment.

(a) Pretreatment Clinical Classification (TNM) – based on evidence acquired prior to the definitive treatment decision.

(b) Postsurgical Histopathological Classification (p.TNM) – based on evidence acquired prior to definitive treatment and the additional evidence acquired from definitive surgery and histopathological examination of the therapeutically resected specimen.

The changes resulting from this decision were incorporated into the Third Edition of the Livre de Poche, published in 1978 in time for the Cancer Congress in Buenos Aires.

At this time (1976) it was also agreed to change a site classification only when new data indicated that the presently published one is unrealistic and in general to retain a site classification for 10 years.

For the pretreatment clinical classification (TNM), the physician must identify and record, at clinical examination before treatment, precise information for each site concerning three components of anatomical extent of disease: the primary tumor (T), the regional lymph nodes (N), and distant metastases (M), using the specified criteria for each. The methods of clinical examination to be used are specified.

To ensure a meaningful classification, appropriate criteria with which to describe the T, N and M categories, and the clinical classes or stage-groups must first have been selected. The criteria selected should be as few and distinct as practicable, should influence prognosis and/or treatment, and should be unmistakable, i.e. not be likely to be interpreted differently by different examiners. Criteria should be chosen which, for the site concerned, offer the best demarcation between the TNM categories and the p.TNM categories and groupings thereof.

In addition of numbers to the T, N and M categories, e.g. T1, T2, T3 and T4; N0, N1, N2 and N3; M0 and M1, indicates increasing degrees of anatomical extent of the cancer and provides a shorthand notation for the particular tumor described.

In most sites four degrees of T are defined and the criteria used for the definition of these categories are usually (not always) size and local extent. In breast, the T-criteria are size in greatest dimension, involvement of the skin, and fixation to underlying tissues; in bladder and stomach the T-categories are based largely on depth of invasion; size is not used.

For each cancer site the regional lymph nodes are defined, e.g. for breast they are the axillary nodes and the supra- and infra-clavicular nodes. Where the regional lymph nodes are accessible to clinical examination, degrees of N are defined, usually four in number (N0, N1, N2, N3). The category N0 indicates that there is no evidence of regional lymph-node involvement, that the nodes are not palpable; N1, N2, N3 describe the clinical state of regional nodes which are palpable, e.g. N1 denotes palpable movable nodes. Where it is impossible to assess the regional lymph nodes clinically the category NX is used.

For the postsurgical histopathological classification (p.TNM), information derived from definitive surgery and histopathological examination of the surgically resected specimen is admissible in describing the pT, pN and pM categories.

While the TNM System has been developed now into a dual-classification system (pretreatment clinical, and postsurgical histopathological), it is the pretreatment clinical classification (TNM), which is of paramount importance for purposes of reporting and evaluation of treatment results. If the results of treatment by radiotherapy are to be compared with those of surgery, the anatomical extent of disease must be established clinically, before treatment.

The final step in the classification process is the grouping of the TNM categories into a small number of clinical classes or "stage groups", usually four in number, which have been discriminating features clinically, distinctive prognoses, and significant implications for treatment.

A detailed description such as that provided by the TNM system is preferable to a summary classification or "staging" for the purposes of clinical assessment, evaluation of prognosis and effective treatment planning. Given a detailed description, any sort of a summary is possible; if you have only a "stage-grouping", a subdivision or a regrouping of cases for clinical research purposes may be difficult if not impossible.

It is an important general rule of the TNM system that the original TNM classification based on pretreatment clinical findings must not be altered when the findings of surgical operation or histopathological examination of removed tumor becomes available; the latter must be considered as an alternative to the clinical classification and not a substitute for it.

If clinicians are convinced that TNM classification serves a useful purpose in treatment planning, assessing prognosis, and treatment evaluation, they will use it. A sytem for general use and international acceptance must serve these objectives and be simple, practical and realistic. The ultimate test is clinical acceptance.

The co-existence of multiple classification methods highlights the need for a single standardized technique for classifying anatomical extent. By applying the TNM system to many sites, the Committee on TNM Classification of the International

Union Against Cancer, the American Joint Committee on Cancer (AJCC) and the national TNM committees in many countries throughout the world have given strong impetus to organized description of the anatomical extent of disease in cancer and have undoubtedly provided a basis for the development of broad international agreement, possibly during this decade.

Any outstanding problems, differences and disagreements about the TNM system can surely be resolved, in Michael Harmer's words, "by patient discussion and negotiation". The objective — international agreement — is within our grasp!

EDUCATION

RISKS OF MEDICAL RADIATION
GORDON RICHARDS MEMORIAL LECTURE 1982*

ERIC J. HALL**, D.Sc., *New York, N.Y.*

The total dose of radiation received by the population is divided up between natural background, medical radiation, and other sources of man-made radiation (Fig. 1). This figure is based on bone-marrow doses taken from the recent report of the National Academy of Sciences on the Biological Effects of Ionizing Radiations (BEIR III), which might be described as the "somatically effective dose" inasmuch as they are the doses relevant to the induction of leukemia. It is apparent that medical radiation now accounts for more than one-half of the dose to the human population in Western industrialized nations. The mean bone-marrow dose from medical radiation, prorated over the entire population, is estimated to be about 92.5 millirems per year. This should be contrasted with the genetically significant dose of only 20 millirems per year from medical radiation. It is much larger because the genetically significant dose arises only from irradiation of younger individuals whereas the somatically effective dose involves irradiation of all members of the population.

With respect to the ratio of risk versus benefit in diagnostic medical radiation, one can compute the number of leukemias resulting from one year's practice of diagnostic radiology in the United States from the product of the mean annual bone-marrow dose, the leukemia risk estimate, and the total population of the United States. These three figures are: mean bone-marrow dose 92.5 millirems per year; the leukemia risk 15-25 cases per million per rem; and the U.S. population about 250 million. The product of these three quantities amounts to (15 to 25) x 250 x 0.0925 = 347 to 678 cases of leukemia. This compares with about 60,000 cases, which occur spontaneously.

Thus, one year's practice of diagnostic radiology in the U.S. provides the benefit of rapid diagnosis to 100 million people but includes the risk of producing 347 to 678 cases of leukemia. To the risk of leukemia must be added, of course, the risk of solid tumors. This is more difficult to estimate because mean organ doses, prorated over the entire population, are not available from the various reports of the Bureau of Radiological Health. Based on the experience with the Japanese survivors of Hiroshima,

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*Abstract from "The Biological Effects of Low Doses of Ionizing Radiations" presented at the Canadian Association of Physicists Congress, held in Kingston, Ontario, June 21-24, 1982.

**Professor of Radiology, Columbia University, New York, N.Y.

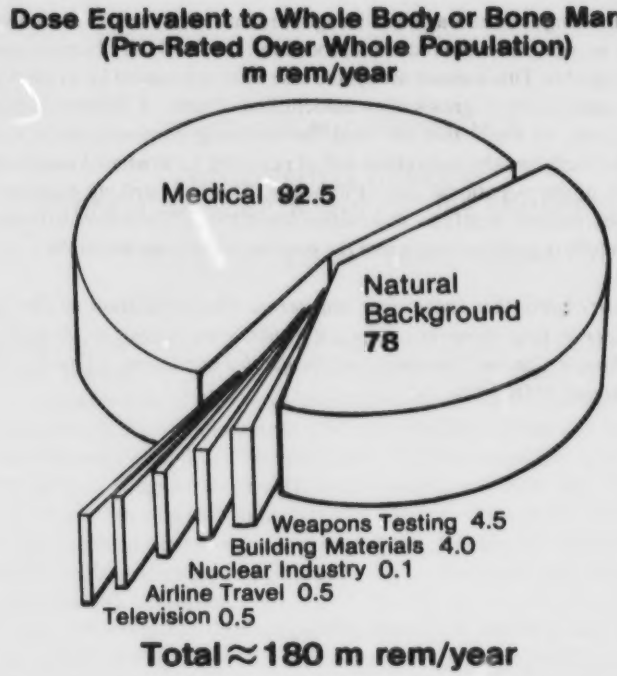

Fig. 1. Bone-marrow doses prorated over the total U.S. population from various sources of radiation, both natural and man-made. Figures taken from the 1981 report of the U.S. National Academy of Sciences on The Biological Effects of Ionizing Radiations BEIR III.

there would be three solid tumors for every leukemia, so that the total risk of cancers might be of the order of 1600 per year. One can make a similar estimate for Canada by assuming a value for the mean bone-marrow dose intermediate between the U.S. (92.5 millirem) and the U.K. (32 millirem) values — say 62 millirem. For a Canadian population of about 22 million, the number of cases of leukemia generated by one year's practice of radiology would then be: (15 to 25) x 22 x 0.062 = 20 to 34 cases of leukemia. The risk-benefit equation for Canada would then read: 10 million patients receiving the benefit of a diagnosis, for a risk of 20 to 34 cases of leukemia produced, and perhaps a total of about 100 cancer cases per year.

While these figures cannot be regarded as better than a "ballpark figure", and are almost certainly a gross overestimate, it is not difficult to conclude that for a patient who is sick and in need of medical care, the risk of carcinogenesis, which amounts to about 1 in 100,000, is a small price to pay for an accurate and speedy diagnosis. In

other words, so long as there is a real and tangible immediate benefit to the individual or to society accruing from the radiation procedure, the small risk of carcinogenesis is clearly acceptable. This is almost always the case when the request for a radiological procedure is part of the diagnosis of an unidentified ailment. A different argument applies, however, to x-rays that are used for screening purposes, where a large number of perfectly healthy individuals will of necessity be irradiated needlessly in order to pick up the occasional case of ill health. The most striking examples are mammography, routine chest films, and routine dental x-rays. These need to be looked at rather carefully in order to ensure that the possible benefit outweighs the potential risk.

(The editor regrets that space does not permit the publication of Dr. Hall's excellent paper in toto, however copies are available on request to: Publications Unit, The Ontario Cancer Treatment and Research Foundation, 7 Overlea Blvd., Toronto, Ontario. M4H 1A8).

22nd CLINICAL CONFERENCE

COLORECTAL CANCER: CURRENT CONCEPTS AND FUTURE PROSPECTS

J. O. GODDEN, M.D., C.M.*, *Toronto, Ontario*

In opening the conference, Dr. D. Laurence Wilson, Dean of Medicine at Queen's University, pointed out that Dr. W. T. Connell, First Professor of Medicine at Queen's, was a member of the Cody Commission whose recommendations led to the establishment of the Foundation. In 1947 the Kingston Clinic was founded and Queen's University established the first chair in radiation medicine. In 1977 the R.C. Burr Wing of the Kingston General Hospital was opened with its own research unit. Dr. Wilson noted that on its 35th birthday the Kingston Clinic is a microcosm of the increasingly sophisticated world of cancer medicine. He said that the presence of the Foundation in Kingston has had a great influence on the development of medicine in general at Queen's University.

In her review of Ontario data concerning cancer, Dr. Aileen Clarke pointed out that an original mandate of the Foundation was the reporting of cancer cases and the recording and compilation of data. With respect to colorectal cancer, it is the second cause of cancer deaths in Ontario. It was responsible for 2000 deaths, that is 14% of all cancer deaths in 1980. It is second only to cancer of the lung in men and cancer of the breast in women. The mortality rates of this cancer have remained unchanged for the last 30 years. She noted that only between 8.5% of cancers of the colon and 15.3% of cancer of the rectum are referred to Foundation clinics in the year in which they are diagnosed. The older the patient, the less likely it is that he or she will be referred.

Dr. Winifred Ross reviewed factors influencing survival. Staging systems are complicated and are not applied uniformly. In the analysis of data on rectosigmoid-junction cancer, of 742 new patients between 1970 and 1979 seen at the Foundation clinics, 50% already had metastatic disease when first referred. The five-year survival for patients presenting with and without metastatic disease is 3% and 35% respectively. Survival is better among patients under age 60 years regardless of the presence of nodal involvement. Adjuvant treatment appeared to increase survival in younger patients, but this therapy needs further research. The present goals are earlier diagnosis, more accurate staging, and improved adjuvant therapy.

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*Editor of Publications, Ontario Cancer Treatment and Research Foundation, Toronto.

Dr. Horatio T. Enterline discussed the pathobiology of colorectal cancer. Colorectal cancer is the product of interplay between dietary and genetic factors, most commonly but not invariably arising within benign adenomas. Its evolution requires many years and, theoretically, we should be able to exercise more effective control than we are now doing. The variation in incidence is not due to ethnic factors but rather to diet-related endogenous carcinogens whose activation is strongly influenced by various microflora. It is estimated that genetic susceptibility accounts for at least 10% of colorectal cancers. The association of ulcerative colitis with colon cancer appears to be a function of the extent of the disease (entire colon) and time (10 years or more). In ulcerative colitis cancer-related dysplasia is distributed in a patchy fashion. For this reason multiple biopsies at suitable intervals may aid in selection of those patients who require colectomy. With regard to the contribution of adenomas, there is good parallelism between the incidence of adenomas and carcinomas in high and low incidence areas of the world. There is evidence that the closer an adenoma is to the rectum, the higher the incidence of areas of dysplasia and of carcinoma within such adenomas. In high-incidence countries, adenomas tend to be larger and, hence, pose a greater danger. Adenocarcinoma is from three to five times as common in patients with adenomas than in those without. There is a direct co-relation between the presence of both the situ carcinoma (dysplasia) and invasive carcinoma to the size of the adenoma. While the incidence of carcinoma in large adenomas is many times that of small adenomas, the number of small adenomas conversely is many times that of large adenomas. It has been well demonstrated that the systematic removal of polyps during periodic sigmoidoscopic examination lowers the incidence of cancer of the colon and rectum. The evidence seems overwhelming that the adenoma-carcinoma sequence accounts for the vast majority of colorectal cancers. Therefore, the presence of an adenoma or especially of multiple adenomas identifies patients at high risk of carcinoma and justifies intense surveillance and removal of identified lesions. The evolution of carcinoma from adenoma is a slow process measured in years — at least five and probably longer. However, by the time a patient develops symptoms, the disease is biologically far advanced.

Dr. W. Robert Bruce, Director of Ludwig Institute for Cancer Research in Toronto, discussed the epidemiology and prevention of colorectal cancer. Diet is important in the etiology of this cancer, particularly at fault may be diets high in meats, fats and low in fibre. A long exposure is needed. Current research is attempting to delineate the events between exposure and the appearance of cancer specifically the sequence of diet, the chemical event, the cellular event and finally the tissue events culminating in cancer over a 30- to 60-year period. Dr. Bruce and his colleagues are seeking "benchmarks" to mark each of these steps. When the Ames test of carcinogenicity was applied to the feces of a Toronto population, it was found that 40% of them have a mutagen, namely, fecapentaene. This mutagen is the product of bacterial action on the contents of the colon. It has been demonstrated that vitamins such as C and E taken by mouth can reduce the concentration of this mutagen. The levels of mutagens in various populations have been established. It appears possible that carcinogens

(left to right): Drs. J. DeCosse, J. W. Meakin, H. T. Enterline, P. J. Froud, S. Fine, W. M. Ross, B. J. Cummings, A. Groll and J. S. Lott.

produced by bacterial action on elements of the diet can damage colonic epithelium by interrupting chromosomal structure. At present the precursor events in colon cancer include the following: inhibition of DNA synthesis and mitosis, development of nuclear aberration, histochemical and cell kinetic changes, the appearance of dysplasia, adenomatous polyps and finally the appearance of carcinomas in situ. In addition to studying the presence of mutagens in the bowel contents and the effect of vitamins and other additions to the diet, Dr. Bruce and his colleagues are doing studies of matched populations after resection of polyps. One group is given a placebo, the other is given 400 mg of ascorbate a day plus 400 mg of alphatocopherol a day. Both groups are then submitted to colonscopy two years later. Compliance is tested by urine examination. By these studies Dr. Bruce hopes to define groups at risk, chemicals which are carcinogens and changes in diet or additives which may prevent cancer induction. A basic problem which remains to be solved is whether the impetus for carcinogenesis comes from the colon side, namely, from agents produced by the action of bacteria on fat, or from the blood stream, that is carcinogens produced elsewhere and brought to the bowel through its blood supply.

Dr. Jerome DeCosse, Chairman, Dept. of Surgery, Memorial Hospital, New York City described his studies in familial polyposis and commented on the value of tumor markers. In respect to the latter he said that except for the CEA test, there are no markers which are reliable. We can only look for historical and other types of markers. Familial polyposis is a genetically-transmitted disease characterized by multiple adenomatous colorectal polyps and a high risk for development of adenocarcinoma. Familial polyposis and Gardner's syndrome should be differentiated from other genetically-linked polyposis syndromes lacking a predisposition for cancer. Total colectomy and ileorectal anastomosis, aggressive follow-up and intensive

surveillance of non-polyp-bearing relatives can reduce the risk of developing cancer. From an epidemiologic point of view, polyposis is a valuable model for the study of the interaction of genetic and environmental factors in the genesis of colon cancer. Nine separate entities have been identified within genetically-linked polypoid disease; however, only five of these carry an increased risk of cancer. The distribution of polyps within the large bowel is important. For example, the distal rectum is not exposed to carcinogens except during the act of defecation. There is substantial evidence that, in familial polyposis, residual rectal polyps frequently regress after colectomy and ileorectal anastomosis. With respect to the risk of cancer in the remaining rectal segment, there is a wide variation in current experience. At the Mayo Clinic the risk of rectal cancer rose with successive years, approaching a likelihood of recurrence of 59% after more than 20 years of follow-up. At St. Mark's Hospital in London, only 2 of 89 patients developed cancer in the retained rectal segment during a similar period of follow-up. In familial polyposis the physician is under an obligation to construct a complete family tree. The asymptomatic descendant or sibling of a polyposis patient should be followed by annual or biennial proctosigmoidoscopy. Because the average interval between the onset of polyps and the appearance of cancers is more than 10 years, endoscopy every two years should suffice. In the absence of symptoms, polyp formation in the rectum, or a positive stool for blood, a barium enema is not necessary as an additional screening procedure. Of 170 patients with active polyposis seen at St. Mark's Hospital, none had a rectum completely free of polyps. In summary Dr. DeCosse said "the war against large bowel cancer is a war against large bowel polyps".

Dr. Aubrey Groll of Queen's University described the role of colonoscopy in screening for colorectal cancer. He noted that, at present, only 40% of all detected colorectal cancers are localized, that is, without lymph-node involvement. The 10-year survival of localized disease is about 67% and, if lymph-node involvement

(left to right): Drs. J. S. Lott, H. T. Enterline and R. W. Bruce.

has occurred, the 10-year survival rate is 35%. When we discover colorectal cancer by chance or by screening asymptomatic patients, the disease is mostly localized and the cure rate approaches 90%. The basis of cancer prevention is the identification of a precancerous condition. The development, in the past decade, of colonoscopy now permits the physician to examine the entire colon and to reach the cecum in over 90% of patients. This instrument permits biopsies and brush cytology of any part of the colon. It is also possible to remove polyps from anywhere in the colon without resorting to laparotomy. Because colorectal cancer is at a relatively advanced stage when most patients seek treatment, some form of screening is essential. Gilbertson and co-workers have shown that cancer of the rectum can be prevented by an aggressive sigmoidoscopic program of polyp detection and removal, however the financial and human cost of this method limits its usefulness. In addition a significant number of polyps and carcinomas occur in the proximal colon out of reach of the sigmoidoscope. Dr. Grolll emphasized that what is needed is a simple, inexpensive, reliable, sensitive and specific test for mass screening. The newly developed, stool hemoccult test is of considerable value to identify those patients who should be subjected to intensive investigation. Shinya and Wolff removed 6000 neoplastic polyps and found and incidence of malignancy of 5%. Morson's rate in London was closer to 10%. Dr. Groll then reviewed the management of colonic polyps. For example, pedunculated polyps on a well-developed stalk, which are benign, are adequately treated by polypectomy. Bowel resection is done if carcinoma extends to the margin of the polyp resection line. Morson believes that colorectal cancer is a slowly evolving disease and that the polyp to cancer sequence may take at least five years, and probably 10 years or longer. Concerning the natural history of polyp recurrence, Henry and co-workers, in a study of 145 patients, found a polyp recurrence rate of 30%. Dr. Groll summarized by saying that the prevention of colorectal cancer is based upon a program which identifies persons at increased risk before they have symptoms. He believes it is feasible to prevent cancer in familial polyposis. Also patients with ulcerative colitis can be managed successfully by current methods. The test of our efforts will be directed to the identification of a large group of patients at increased risk of cancer of the large bowel; these require regular follow-up.

Dr. Ralph Blend spoke about the application of CT scanning to the management of colorectal cancer. In Class 1, as an early diagnostic procedure to detect the primary tumor, it is only by accident that the lesion is caught in an "axial cut" due to the complex anatomy of the bowel. In Class 2, the patient has CT to define tumor extent after surgery. Here the radiologist must cope with the effects of the surgical procedure especially in the pelvis. Class 3 relates to a search for pelvic or para-aortic modes. The final two classes involve examination of liver, brain or lungs for metastasis and finally CT is done in the planning of radiation therapy to locate the tumor and to make judgements about the alteration of fields. In the differential diagnosis of recurrence, a CT-guided biopsy is of great value. It may also detect retroperitoneal involvement in patients with leg pain or detect metastases and distinguish these from other changes in the liver.

Dr. Gunes Ege described the applications of radionuclide scanning in the management of colorectal cancer. Iliopelvic lymphoscintinigraphy has demonstrated its effectiveness in the early detection of metastasis, in central pelvic lymph nodes. Perianal injections of the colloid demonstrates pelvic lymphatics which drain via the sacral and common iliac nodes to the para-aortic nodes. Within two years of the development of this technique in 1977, Dr. Ege was able to review the experience in 184 patients referred to the Princess Margaret Hospital with varying stages of diverse pelvic neoplasms. Although no histopathologic correlation could be carried out, clinical corroboration was obtained in 60% of cases. Experience since that time has modified the criteria used for the interpretation of the lymphoscintigram. The correlation is good between the results of the examination and the stage of the disease. In early primary and extensive primary rectal carcinoma, corroboration is obtained in 73% of the lymphoscintigrams. To date, Dr. Ege and her colleagues have studied 1043 patients with varied pelvic neoplasms. Ongoing studies are aimed at obtaining surgical pathological correlations of the iliopelvic scintigrams. It is hoped that these will shed further light on the sensitivity and specificity of this particular technique.

In a panel on the treatment of colorectal cancer, Dr. Jerome DeCosse spoke about the role of surgery, Dr. Bernard Cummings of the Princess Margaret Hospital covered the role of radiotherapy, and Dr. Sheldon Fine, also of the Princess Margaret Hospital, spoke about the role of chemotherapy. Dr. DeCosse said that such treatment now was chiefly surgical but "it's not going to get much better". In such surgery the operative mortality is about 6% and deaths due to infection are about 2%. Dr. DeCosse practises extensive mesentery resection in association with excision of the primary. In his view, the major advance has been the preservation of a functional sphincter of the rectum. In the recent past excision of the sphincter has steadily declined and restoration has increased. There is, as yet, no consensus concerning which patient should get preoperative radiation or chemotherapy. Staging requires an operation and traditional staging procedures are in considerable confusion. In Dukes' classification survival is a reciprocal of advancing grade. The results show a relationship between direct extension and lymph-node involvement. A choice of surgical treatment leans heavily on the pathologist's advice after his examination of a specimen taken in local excision. The significant factors are: depth of invasion; clearness of margin; and degree of differentiation of the tumor. Dr. DeCosse believes that adjuvant radiation therapy has an important contribution to make in the treatment of this disease. He prefers postoperative radiation. He believes preoperative treatment sets up adhesions and small-bowel complications.

Concerning the radiation therapy of colorectal cancer, Dr. Cummings said that curative treatment was directed at rectal tumors. Its use in colon cancer is only palliative. Radiation is used to improve survival, reduce tumor size before operation, reduce local recurrence rate, and reduce distant metastasis. In many patients the number of positive lymph nodes is reduced. However, reduction in pelvic recurrence may mean little if distant metastases are unchanged. It is still an open question whether radiation therapy can convert an unresectable tumor to a resectable lesion.

Drs. J. DeCosse, H. T. Enterline, S. Fine, P. J. Froud, B. J. Cummings, W. M. Ross and A. Groll.

Adenocarcinoma of the rectum is among the most common malignant tumors in Ontario; it develops in about 20 persons in every 100,000 each year. One-half of these patients have tumors that are too extensive to resect, or develop local recurrence in the pelvis following surgical removal, which initially appeared to be complete. The palliative benefits of radiation for these local tumor masses have been recognized for many years. Current research is being directed to reducing the incidence of pelvic recurrence following surgical resection of primary tumor, and to identifiying patients in whom radiation can completely destroy the rectal tumor enabling the therapist to preserve the rectum and anal sphincter. Radical radiation therapy in rectal cancer uses two techniques: intrarectal or "Papillon" technique and external-beam therapy. The first is used for accessible tumors within 10 to 12 cm of the rectum. These must be small, exophytic, mobile and well-differentiated. With external-beam therapy, the five-year survival is 38% with mobile tumors, and 23% with fixed tumors. The primary objective of radical radiation is to avoid abdominoperineal resection. In the PMH experience it has been seen that the tumor may not regress for up to six months. In the immediate future the major needs in this area are: a good clinical staging system, and data which will answer such questions as: Do we need complete clinical regression? How long can we defer surgery? All agree that there is great need to standardize surgical procedures and to explore the interaction of radiation and systemic chemotherapy.

With respect to the role of chemotherapy, Dr. Sheldon Fine said that so far this is "an unproven modality". Dr. Fine reviewed survival in terms of various criteria and reported that his results with 5-FU gave an approximate 10% response rate. The addition of second and third drugs does not appear to increase survival. Research in

the future will be directed at developing new drugs and to improving our use of current drugs especially 5-FU. In summary he said we need new drugs designed from a knowledge of the biology of colorectal cancer.

The final panel of the conference was that concerning current concepts and future prospects. Under the chairmanship of Dr. John Gutelius, Professor of Surgery at Queen's University, Drs. Bruce, DeCosse, Enterline, Cummings, Fine and Groll responded to questions from the audience. Concerning the Feinstein staging by symptoms, Dr. DeCosse said that he had never understood it. Dr. Cummings said that at PMH it had been used retrospectively and found to have some value. From a history review he and his colleagues found that there were definite prognostic groups even though they had identical Dukes' stages. He noted that you can demonstrate similar differences using CEA staging. In response to a question concering the value of preoperative radiation plus 5-FU, Dr. Fine said that he doubted 5-FU alone could have much effect. There was considerable interest in the benefits of mass screening. Dr. Groll believes that the best technique is three consecutive hemoccult tests on an appropriate test diet. He notes that 10 to 12 cc of blood are needed for a positive test. Technicians can do the actual tests; the rate of false positives is high but the test is a good one. Dr. Bruce believes that these screening tests should be done in association with a clinical study. Currently a pilot study in Toronto is looking at the effect of diets on the development of polyps. Dr. Cummings noted that there are 6.8 million Canadians over the age of 40 at risk. He does not believe that hemoccult screening can identify polyps and it misses 15% of patients with cancer. Indeed many patients regard occasional blood in the stool as normal. Dr. DeCosse summarized by saying that screening should focus on high-risk patients and it should be done in association with other health assessments. Concerning the value of radical lymph-node dissection, Dr. DeCosse said that he believed in it but couldn't prove its value. He said it is a great weakness of surgical treatment that surgeons don't all do the same operations and, indeed, individual surgeons do not do the same operation each time. This makes evaluation and comparison extremely difficult. The question: "If you had a Dukes' B lesion in your rectum, what treatment would you choose?" drew the following replies: "I would ask for high-dose preoperative radiation therapy. If the tumor was stable on follow-up, I would observe. If it enlarges, I would resect it." Dr. DeCosse said "If it is bulky primary, do preoperative radiation and then resection." Concerning the complications of external beam, radiation therapy, Dr. Cummings said that of 123 patients, 2 had died of radiation enteritis. Concerning invasion of a stalk that has no clear margins and was removed by a snare, Dr. DeCosse said "If it is well differentiated, I would leave it alone". Dr. Groll said "If the muscularis mucosa has been invaded, I would call the surgeon". Someone asked about the management of isolated recurrent rectal cancer and the use of CEA in follow-up. Dr. DeCosse said that if it is an inward growth of local pelvic metastasis, it is incurable. Pain, even after two years, represents recurrence. The treatment, which is palliative, is radiation. Dr. Cummings said that at PMH, he and his colleagues do not seek confirmation with needle biopsy; they used the CT scan. Someone asked "Will radiation therapy and

some-as-yet-unidentified chemical make abdominoperineal resection a thing of the past?" Dr. Cummings replied: "No, the abdominoperineal is a good operation although it may not always be the best first procedure." Finally, regarding screening, a panel member summarized by saying: "The hemoccult test is the only game in town, but it is not ideal. A young Ph.D. with a background in protoporphyrin metabolism could become famous with a better screening test".

Dr. J.W. Meakin, the Executive Director of the Foundation, summarized by thanking the U.S. visitors, by thanking other speakers, by congratulating the Kingston Clinic on its 35th birthday, and by thanking Dr. DeCosse for the Bert MacLaren Lectureship. He said that, despite the grim statistics, he detected a note of hope. Dr. Clarke had used the available cancer data to the best advantage but more complete data were necessary to provide meaningful information. Dr. Enterline confirmed that the sequence – adenoma to carcinoma – is a natural one in our present environment. Dr. Bruce has encouraged us to hope that a good assay for colorectal cancer is coming on line. Dr. Meakin noted that screening and clinical advance in diagnosis and management, and notes with approval that surgical procedures and radiation are slowly integrating themselves. But, as Dr. Fine pointed out, chemical therapy is not yet making its contribution.

SUMMARY OF OCF EDUCATION ACTIVITIES

Manpower Shortage of Oncologists in Ontario

In 1982, the Foundation continued its efforts to ameliorate the serious shortage of practising radiation oncologists and medical oncologists in Ontario. While progress has been made, further improvement will require a major commitment (both philosophically and fiscally) from both the Foundation and the Ontario medical schools.

Historically the subspecialty of oncology has fared poorly in the competition among the various subspecialties within the universities for the training "slots" awarded to the universities by the Ministry of Health. In addition, most graduating physicians have not perceived the field of oncology as attractive. As a result, the training programs in Ontario and Canada, in the past, have not produced sufficient number of oncologists to meet the demand and still do not. This deficiency has been met by attracting these specialists from abroad (albeit at no cost to Ontario and without competing with Canadian-trained oncologists). However, as indicated in *Cancer in Ontario* 1981, expanded and improved undergraduate and postgraduate educational programs in oncology at the Ontario medical schools with appropriate fiscal support would provide the best longterm solution.

The Foundation has been in close consultation with the Ontario medical schools and also recently informed the Task Force on Medical Manpower of the Ontario Council of Health concerning the serious shortage of manpower in oncology. (The Task Force is examining the Province's future needs for physicians and is making recommendations to the Ministry of Health.) We hope that recommendations arising from this study will assist the Foundation in correcting, as quickly as possible, the chronic shortage of oncologists in Ontario. Our readers may be interested to know that currently 70% of all radiation oncologists in Ontario and 30% (as of 1980) of all medical oncologists are foreign medical graduates. Obviously this manpower shortage cannot be allowed to continue, particularly in light of the approaching retirement of several of the Foundation's senior staff who have been the cornerstone of the Foundation's system of oncological services for many years.

In part through the Foundation's efforts, the Council of the Royal College of Physicians and Surgeons of Canada has granted formal recognition to medical oncology as a subspecialty and has approved certification in this important field. This designation will be a Certificate of Special Competence based on previous certification in internal medicine or hematology. It is hoped that this formal recognition will make the subspecialty more attractive to physicians. It is encouraging to note that radiation oncology is one of the subspecialties recently identified by both

COFM (Council of Ontario Faculties of Medicine) and the Ministry of Health as suffering from a manpower shortage.

By means of an "add-back" approach to residency posts, the Ministry will provide support for a number of posts in designated specialties suffering from manpower shortages (one of which has been confirmed as "radiation oncology"). These posts will be shared among the medical schools on a pro rata basis in 1983.

The Foundation is urging each of the Ontario medical schools to allocate at least three "add-back" residency positions to radiation oncology (a three-year training program). The University of Toronto has responded positively, increasing its already strong support of the clinical oncology program centered at Princess Margaret Hospital and Toronto-Bayview Clinic from 15 to 17 positions. Budding programs at University of Western Ontario, McMaster University, and University of Ottawa have been strengthened by a decision to allocate one, two and three positions respectively.

While the Foundation has funded residency positions in radiation oncology at several clinics, we now face not only increasing fiscal constraints but also requests for support of some residents in medical oncology and for "fellowship" support. All of this is in addition to our support of summer students and undergraduate electives.

The Revised Ivan H. Smith Program

In 1982, in co-operation with the Ontario Division of the Canadian Cancer Society, the Foundation again supported studentships for medical undergraduates working in one of the regional treatment centres, namely Hamilton, Kingston, London, Ottawa, Thunder Bay, Toronto-Bayview, and Windsor, and the Princess Margaret Hospital. To fit in with the curriculum demands at each of the province's five medical schools, the flexibility of these awards (now known as Ivan H. Smith Memorial Studentships) was increased in 1982. These studentships are now open to any student in an Ontario faculty of medicine and may be held from a minimum of 4 continuous weeks to a maximum of 12 continuous weeks at any time after the student has completed his/her second medical year and before graduation. The major factor in the awarding of the studentships is academic achievement.

The impact of this increased flexibility in these awards was felt in 1982 when 23 studentships were awarded (compared to the 10 Ivan H. Smith Memorial Scholarships and 4 Ontario Cancer Foundation Bursaries awarded in 1981). All of the students took their studentships in one of the Foundation clinics or the Princess Margaret Hospital, except one student from Queen's University who, by special arrangement, took his elective at Memorial Sloan-Kettering Cancer Center in New York City. These studentships introduce the future physicians of Ontario to the many rewarding aspects of a career in oncology by giving them an opportunity to observe and participate in the clinical and research activities at the regional treatment centres.

Increased Need for Medical Physicists

The field of oncology requires a broad application of high technology viz. CT scanners, ultrasound, and the newly emerging nuclear magnetic resonance imaging

process, etc. in the planning and delivery of treatment, and in research. In response to the need for increasing numbers of specialists in physics, capable of applying the latest technology to clinical medicine, the Foundation announced, in *Cancer in Ontario* 1981, the creation of graduate and postdoctoral fellowships in medical physics. As a result of the March 1982 competition, we awarded two Graduate and one Postdoctoral Fellowships in Medical Physics (named in honour of Dr. Harold E. Johns, O.C.).

For the second year, the Foundation offered Summer Studentships in Medical Physics (also named in honour of Dr. Johns) to be taken at the Princess Margaret Hospital and at the Foundation's clinics throughout Ontario. This program was designed to encourage a greater number of high-quality Ontario students, now pursuing undergraduate courses in physics or related disciplines to consider a career in medical physics as it is applied to oncology. Twelve of these studentships were awarded for 1982.

The Foundation was pleased to be able to offer the foregoing fellowships and summer studentships in medical physics (made possible through a special cancer services improvement grant to the Foundation by the Ontario Division of the Canadian Cancer Society) for the purpose of increasing the complement of medical physicists practising in Ontario.

Continuing Professional Medical Education

An active program of continuing education, supported financially by the Foundation, goes on at the clinics and the Princess Margaret Hospital throughout the year. Clinical days and seminars were organized, guest lectures hosted, and numerous lectures were given in the community by members of the clinic staffs.

Annual lectures funded by the Foundation in 1982 were the Gordon Richards Memorial Lecture, the W. G. Cosbie Lecture, and the Bert MacLaren Lecture. The Gordon Richards Memorial Lecture was delivered at the Congress of the Canadian Association of Physicists in June 1982 in Kingston; the lecturer, Dr. Eric Hall, Professor of Radiology, Columbia University, New York, spoke on the topic "Relative Risks of Low-Level Radiation". The W. G. Cosbie Lecture was delivered at the meeting of the Canadian Oncology Society, which was held in conjunction with the NCIC Clinical Trials Meeting in Montreal in November 1982; the lecturer Dr. R. B. Livingston, spoke on the subject "The Treatment of Patients with Regional Unresectable Non-Small Cell Carcinoma". The Bert MacLaren Lecture was delivered during the 22nd Clinical Conference hosted by the Foundation in Kingston, Ontario, on October 19, 1982. Dr. Jerome J. DeCosse, Chairman, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York City spoke on "Studies in Familial Polyposis and Tumor Markers" (the conference was titled "Colorectal Cancer — Current Concepts and Future Prospects").

The Harold Vail Visiting Professorship was established at the Ottawa Clinic in 1979 through a generous donation from the late H.G. Vail. The first visiting lecturer, Dr. Saul Rosenberg, Professor of Medicine and Radiology, Stanford University,

spent December 16 and 17, 1981 in Ottawa, participating in medical grand rounds at both the Civic and the General Hospitals. The titles of his presentations were "Non-Hodgkin's Lymphoma: Classification, Prognosis and Treatment" and "Hodgkin's Disease – Increasing Role of Multimodality Therapy". On October 22, 1982, the second visiting lecturer was Dr. Ervin Epstein, dermatologist from Oakland, California, who presented an address entitled "Malignant Melanoma – the Black, the White and the Grey".

Two Ontario Cancer Foundation Lectures were given in 1982. On September 24, Dr. Edwin R. Fisher, Professor of Pathology, University of Pittsburg, spoke at the annual convention of the Ontario Association of Pathologists in Peterborough; his subject was "Pathologic Considerations Concerning the Evolution, Prognosis, and Treatment of Breast Cancer". The Foundation contributed to the course "Women and Illness" presented by University of Toronto Faculty of Medicine and the Women's Clinics of the Toronto Western Hospital and Sunnybrook Medical Centre. This international symposium was held at the Park Plaza Hotel, in Toronto, on November 5 and 6, 1982. With its support, Dr. E. Small spoke on the subject "Female Sexuality and Cancer".

On October 4, the Foundation supported the oncology theme at the 20th Annual Scientific Meeting of the Ontario Chapter, College of Family Physicians of Canada. Dr. L.M. Tarshis, Assistant Professor, Department of Otolaryngology, University of Toronto, chose as his topic "A Lump in the Neck"; Dr. C. Cripps, Medical Oncologist, Ontario Cancer Foundation, Ottawa Clinic, spoke on "Cancer Clinics and Family Physician Communication"; and Dr. L. From, Pathologist-in-Chief, Women's College Hospital gave an illustrated lecture on "Skin Cancer".

In 1982, the departments of continuing education at Ontario medical schools received financial support for continuing postgraduate educational programs with a significant cancer content.

Cancer Information Resource Centres

As regional treatment centres, the Foundation's clinics and the Princess Margaret Hospital are logical information sources for oncology-related queries. Consideration is being given to the establishment of a referral network within each of the Foundation clinics, which would be managed by the Foundation and serve as a resource for the media, public, physicians and their cancer patients.

Mary Lou Erochko
Administrative Assistant

REGIONAL TREATMENT CENTRES

REGIONAL TREATMENT CENTRES

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ONTARIO CANCER FOUNDATION HAMILTON CLINIC

HENDERSON GENERAL HOSPITAL

Director:

W. M. Hryniuk, M.D.

Radiation Oncologists:

V. R. Basrur, Ph.D., M.D.
W. Muirhead, M.B., Ch.B.
A. F. Phillips, M.B., Ch.B.
I. Z. Strautmanis, M.D.
A. A. M. Tadros, M.B., B.Ch.

Medical Oncologists:

G. P. Browman, M.D.
A. T. Figueredo, M.D.
M. Levine, M.D.
P. B. McCulloch, M.D.

Physicists:

C. Kwok, Ph.D.
V. G. Peters, B.Sc.
R. H. Price, B.Eng.
B. C. Wilson, Ph.D.

Business Manager:

Catherine E. Squires

Senior Radiotherapy Technician:

Beverly J. Walker, R.T.

Nurse Administrator:

Heather B. Porter, B.N.Sc.

Senior Medical Records Officer:

Denise Armstrong (acting)

During the past year, Dr. Mark Levine has joined the Department of Medical Oncology, and Dr. Cheuk Kwok and Mr. Arnold Herer (in training) joined the Department of Physics. Mrs. Heather Porter has joined the clinic as Nurse Administrator. Mrs. Betty Ho left the clinic to become Head Record Librarian at Toronto General Hospital.

A decision to build a new lodge for patients on treatment has been endorsed by the Canadian Cancer Society, Ontario Division, and by the District Health Council; the Hamilton Civic Hospitals Board is willing to provide the land. Architect's plans are now being drawn up. The lodge will be of great help to patients who come to the clinic from a distance and will be particularly valuable to those receiving radiation with multiple fractions each day.

The Ministry of Health has approved construction of a concrete bunker to house a new 25 MeV linear accelerator (Thorac 25) and approval has been obtained for on-site reconstruction of our 20-year old 6 MeV linear accelerator. This arrangement will allow uninterrupted service to patients.

With the helpful advice of Atomic Energy of Canada Ltd., the physics department has modified our Theratron 80 cobalt unit so that it can be rigged for whole body radiation with a vertical high-dose rate beam, and still return to its normal rotational mode the same morning. This will enable us to duplicate the whole body radiation given at Princess Margaret Hospital in Toronto, and will allow further development of the bone-marrow transplantation program.

The Ministry of Health has approved the acquisition of a whole body CT scanner for the Henderson Hospital, our host hospital. The scanner, which was purchased by Hamilton Civic Hospitals out of their own funds, will make a major contribution to cancer treatment planning. In addition, a new gamma camera with capability of three-dimensional localization of lesions using computed tomography will bring the Department of Nuclear Medicine at the Henderson Hospital to the state of the art.

Radium insertions have been transferred to the main hospital operating room and the previous operating suite has been redesigned for outpatient chemotherapy.

Dr. B. Trossman, a psychiatrist, and Dr. Elizabeth Latimer, a physician active in pain control and palliative care, have instituted a comprehensive psychosocial support program for cancer patients both in the clinic and on the oncology ward. In the Department of Nursing, Mrs. K. Kiehl, who is studying for a certificate in behavioural sciences, provides relaxation therapy for selected patients. In addition, the introduction of primary care nursing — with the clinic nurse as a member of the therapeutic team — allows our nurses to participate in control of symptoms such as nausea, vomiting, and pain.

The outreach clinics using the Ontario Cancer Foundation's record-keeping system are now operating in St. Joseph's Hospital, and in McMaster University Medical Centre. Dr. Mark Levine has assumed responsibility for co-ordinating the clinic at St. Joseph's, and Drs. Peter McCulloch and David Clark supervise the activity at the Medial Centre.

Volunteers are now active in patient escort and in the messenger service. These volunteers receive a short period of training and we planned a program of continuing education.

Developments in nursing education include a basic course in oncology nursing for registered nurses at McMaster University. All registered nurses at the Hamilton Clinic, who have not had this training, are enrolled in the first class (January to April 1983). In addition, selected senior students in the Department of Nursing at Mohawk College obtain clinical experience at the clinic after a learning unit at the college entitled "Introduction to Oncology".

In the area of research, several oncology nurses are participating as investigators in a project designed and managed by Ms F.A. Kraiker, R.N., who is completing the Master of Health Sciences Degree at McMaster University.

Our monthly clinical trials dinner meetings provide basic scientists, clinical oncologists, and visitors with an opportunity to review the clinic's results site by site and constitute a forum for the discussion of ways of improving these results. These discussions, particularly those concerning future lines of research, continue to be lively and productive. After an experience of two and one-half years with this program, we are repeating reviews of each site to see if changes in treatment policy resulting from the first clinical trials dinners have improved survival. Changes in treatment policy developed at the 1979 meeting have improved survival of poor prognosis lymphomas from 40% to 80% at two years. In breast cancer, premenopausal one- to three-nodes positive, disease-free survival has improved on new adjuvant treatments from 70% to 100% at two years. No improvements have occurred in other patients with breast cancer: premenopausal greater than three-node positive — still 45% disease-free survival at two years; Stage IV breast cancer still 40% survival at two years. In these latter categories, treatment policies have been changed once more.

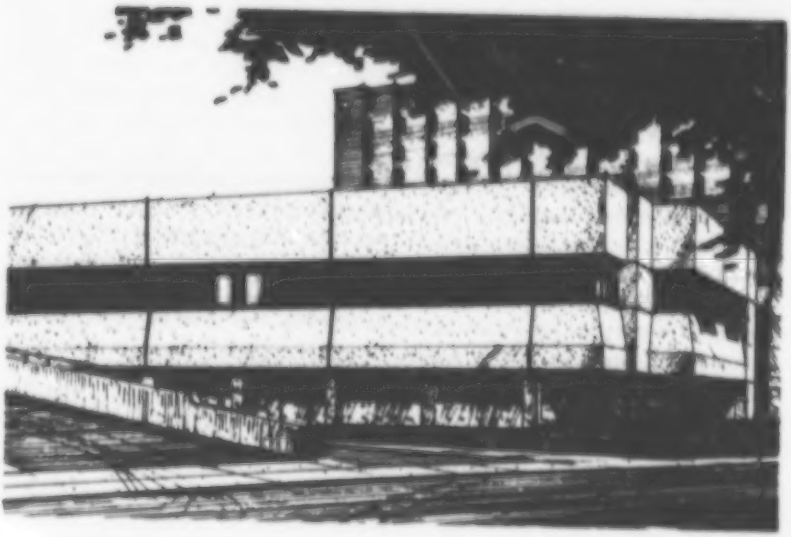
New developments in cancer therapy have made clinical investigation an essential part of all cancer treatment programs. The Hamilton Clinic now has 306 patients on local clinical trials and 170 on national trials. These studies, assisted by one full-time clinical trials secretary, and four full-time nurse oncologists are described elsewhere in this report.

Oncology rounds, which are held weekly, are based on multidisciplinary participation by clinicians and basic scientists. The emphasis is on the application of basic science to clinical oncology. In addition, a weekly basic science seminar is held with participation of undergraduate and postgraduate students. Our visiting professor for 1982 was Dr. James Holland, Chairman of the Department of Oncology at Mount Sinai School of Medicine in New York.

W. Muirhead, M.B., Ch.B., D.M.R.T., F.R.C.P. (C)
Senior Radiation Oncologist

ONTARIO CANCER FOUNDATION KINGSTON CLINIC

KINGSTON GENERAL HOSPITAL



Director:

J. S. Lott, M.D.

Radiation Oncologists:

P. J. Froud, M.B., Ch.B.
Vera L. Kraus, M.D.
Winifred M. Ross, M.D.

Medical Oncologist:

J. L. Pater, M.D.

Career Scientists:

J. C. Kennedy, M.D.
H.F. Pross, M.D.

Clinical Assistants:

Mona D. Mulligan, M.B., Ch.B.
Diane Pross, M.D.

Physicists:

Jean Robins, M.A.
P. C. Shragge, Ph.D.

Honorary Medical Consultant:

R. C. Burr, M.D.

Business Manager:

R. J. Good

Senior Nurse and Radiotherapy Technician:

E. Marguerite Bolster, Reg.N., R.T.

Social Service Nurses:

Ruth Crafts, Reg.N.
Karen Gill, Reg.N.

Senior Medical Records Officer:

R. S. Walker

Lodge Supervisor:

Nancy G. Ambury

We have experienced an unusual surge in the number of new patients with malignant disease referred for management advice during the past year; our current figure is more than 12% ahead of the corresponding figure for 1981. The exact reasons for this change are uncertain but, in part, it reflects the increasing awareness of physicians that adjuvant therapy may benefit their patients, and the gradual increase in the number of people entering their cancer-bearing years. This trend has been forecast for some years, hence we anticipate that referrals for malignant disease will continue to rise steadily over the next several years.

In view of the increase in our malignant disease workload, we look forward to the arrival, in January 1983, of a new medical oncologist – Dr. Barbara Campling, and, at the same time, to the part-time appointment of Drs. Peter Galbraith and David Ginsburg of the Queen's University hematology/oncology division. Plans are being developed to move the Kingston General Hospital outpatient chemotherapy unit into the OCF Kingston Clinic. We hope this move will coincide with the commencement of the new medical oncology appointments so that most of the area's nonsurgical oncology treatment can be provided under one roof – an invaluable team experience with educational benefits to patients, nurses and physicians alike.

Currently, three of our postgraduate residents are sitting their Royal College examinations in radiation oncology, and we wish all of them well, now and in the future. In the coming year, we hope to attract at least three promising candidates to our residency program in radiation oncology. We anticipate that this program will be strengthened considerably by the proposed alliance between this clinic and our Ottawa colleagues in postgraduate education. Judging by our workload figures alone, we shall need all the trained oncologists we can attract in this province for many years to come; in this connection we hope that increasing numbers of Canadian medical graduates will be attracted to oncology by these expanded programs. Our strong undergraduate oncology teaching program is being received with increasing enthusiasm and, during their training, many medical undergraduates seek to work in the cancer clinic for as long as possible.

As in other clinics, the current and continuing shortage of oncologists here is matched by the shortage of medical radiation technologists. We have said farewell to another of our number this year, and continue our efforts to attract technologists to Kingston to replace them, so far without success. Fortunately, we have an excellent

team of nurses, who assist with our clinical work and their efforts do much to meet the increasing demands for patient care.

The Kingston Division of Medical Physics is continuing with its program of research and development; this includes measurements of the shape of the unflattened linear accelerator beam, and the magnitude and nature of the scattered radiation arising from the collimators. The information obtained will be used to design our improved flattening filter for the Therac 20. The team also plans to implement a microcomputer-based system for recording patient data on the Therac 20 machine.

Our congratulations go to Dr. Stewart Lott on his election as the Vice-President (Radiation Oncology) of the Canadian Association of Radiologists, and to Dr. J.L. Pater, the Director of the Clinical Trials Group of the National Cancer Institute of Canada in Kingston, on the successful transfer and productive continuation of this important undertaking.

P. J. Froud, M.B., Ch.B., D.M.R.T., F.F.R., F.R.C.P. (C)
Senior Radiation Oncologist

ONTARIO CANCER FOUNDATION LONDON CLINIC

VICTORIA HOSPITAL

Director:

H. Bush, M.B., B.S., Ph.D.

Radiation Oncologists:

W. Allt, M.D.
P. Banerjee, M.B., B.S.
A. Cheung, M.D.
J. A. Gilchrist, M.B., B.S.
T. A. Watson, M.B., Ch.B.

Medical Oncologists:

G. Cairncross, M.D.
W. I. Kocha, M.D.
L. Levin, M.B., Ch.B.
R. C. Lohmann, M.D.
J. Skillings, M.D.
D. F. White, M.D.

Physicists:

D. J. Dawson, Ph.D.
M. Gribble, M.Sc.
J. C. F. MacDonald, Ph.D.

Experimental Oncologist:

W. R. Inch, Ph.D.

Business Manager:

E. Micallef

Administrative Assistant:

Christine Harman, M.H.A.

Senior Nurse:

M. Elaine Marshall, Reg.N., R.T.(T)

Senior Radiotherapy Technician:

Margaret Stepanek, A.C.(T)

Senior Medical Records Officer:
Dorothy V. Wickett

Lodge Supervisor:
Jean Stewart, Reg.N.

In the past year, the clinic experienced an increased caseload with respect to both chemotherapy and radiotherapy. The added demands on the medical staff were eased somewhat by the arrival of four additional medical oncologists – Drs. G. Cairncross, W.I. Kocha, L. Levin, and J. Skillings, and one radiation oncologist – Dr. W. Allt. We remain short-staffed with respect to radiation therapy, and the search continues for additional radiation oncologists.

Space continues to be a problem because adequate funds for the refurbishment of the clinic have not been forthcoming. Nevertheless, planning for a new clinic is continuing and will remain a high priority in the coming year.

Earlier this year, through the medical school of the University of Western Ontario, the clinic was awarded a grant from the Terry Fox Special Cancer Research Fund, which will be used for the construction of four additional research laboratories, and for upgrading of the clinic's animal facility. Three of the four available positions funded from the Terry Fox Fellowship Training Program awarded last year have been filled by two MDs – J. Gardner and G. Bondy, and one PhD – J. Smith. Two of the fellows will be sited at the London Clinic and the remaining two will be sited at the Cancer Research Laboratory of the University of Western Ontario.

The clinic's commitment to basic and clinical cancer research is increasing with the arrival on staff of individuals active in investigative cancer medicine. Shortly we will be welcoming Dr. A. Chambers who will be joining our ranks as a career scientist. A second 6 MeV linear accelerator was installed in November, and planning is underway for the expansion of the present simulator suite to accommodate a Therasim 750 scheduled to arrive in the spring of 1983.

Approval has been given by the Joint Lodges Committee for the expansion of Thameswood Lodge to increase its bed complement to 50 beds from its present 30 beds, and to expand its recreational and leisure areas. We are hoping for completion of this project by spring 1983.

Approval in principle has been given by the Foundation Head Office for the establishment by this clinic of an outreach program at St. Joseph's Hospital in London and for the appointment of a medical oncologist, Dr. J. Skillings, to act as co-ordinator. The implementation of this program is contigent, of course, on approval and granting of funds to the Foundation by the Ontario Ministry of Health in the spring of 1983.

The London Clinic has been selected as one of 10 centres across Canada to participate in the National Study of Breast Screening being co-ordinated by the National Cancer Institute of Canada. The target screen for this centre will be 4500 women over a one or two-year period, continuing with rescreening examinations over four to five years. We expect to start early in the new year.

We are collaborating with the Hamilton Clinic in the development of a joint postgraduate training program in radiation oncology, which would operate out of the two clinics. Candidates would be selected jointly and the program would make use of facilities and personnel from both sites.

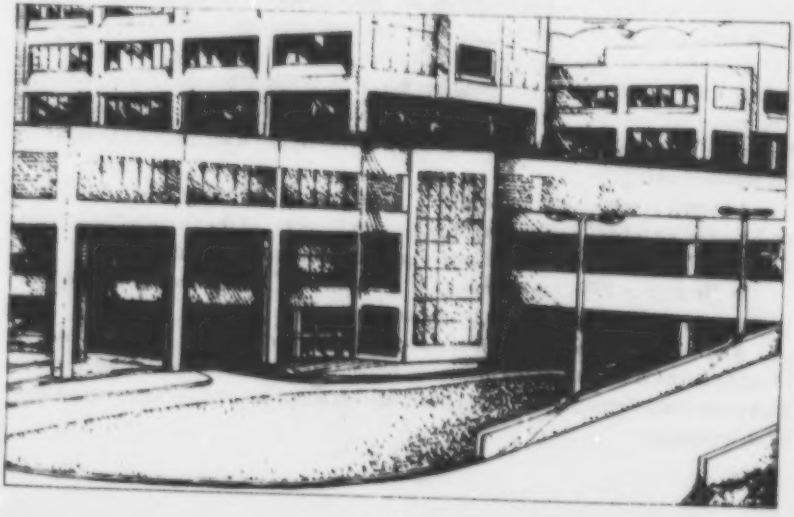
The clinic gratefully acknowledges the assistance of the London-Middlesex Unit of the Canadian Cancer Society and most particularly its volunteers. We are most appreciative of the indispensable services they provide to cancer patients and their families.

Christine Harman, M.H.A.
Administrative Assistant

ONTARIO CANCER FOUNDATION OTTAWA CLINIC

OTTAWA CIVIC HOSPITAL

AND OTTAWA GENERAL HOSPITAL



Acting Director:

G. E. Catton, M.B., B.S.

Radiation Oncologists:

A. F. Crook, M.B., B.Ch.
C. J. E. Danjoux, M.D.
Rebecca S. R. McDermot, M.D.
J. T. Nichol, M.D., Ph.D.

Medical Oncologists:

Christine Cripps, M.D.
W. E. Hirte, M.D.
J. A. Maroun, M.D.
D. J. Perrault, M.D.
D. J. Stewart, M.D.
L. L. Stolbach, M.D.
V. P. J. Young, M.D.

Physicists:

L. H. Gerig, M.Sc.
P. M. Pfalzner, M.Sc.

Honorary Medical Consultant:

T. G. Stoddart, M.D. (to October 1982)

Business Manager:

S. McAdam

Senior Nurse:

Cora J. MacMillan, B.Sc.N.

Lodge Supervisor:

June M. Davidson, Reg.N.

Senior Radiotherapy Technician:

R. P. Wallace, A.C.(T)

Senior Medical Records Officers:

M. Constance Therrien (Civic Hospital Division)
Madeleine M. Brassard (General Hospital Division)

Over the past year, several important staff changes have taken place. Dr. M.E. Tulloh resigned as Director of the Clinic effective January 31, 1982 and has returned to the United States. Dr. Gordon E. Catton has been appointed Acting Director and a search committee is now in place. In October 1981, Mr. Sam McAdam joined the staff as Business Manager. In November Mr. Ron Wallace became the new Chief Technologist coming to Ottawa from the Princess Margaret Hospital in Toronto. In December Dr. Robert Baker retired as Chief Physicist and a search is underway for his replacement.

A memorial service was held for Dr. T. Glen Stoddart at Christ Church Cathedral on Monday, October 25, 1982. Dr. Stoddart was Director of the Ottawa Clinic from 1952 to 1978 when he retired and was appointed Honorary Consultant.

In December 1981, ten members of the staff and five retirees of the Ottawa Clinic received the Foundation's Long Service Award.

A new sophisticated telephone system was installed in the Civic Hospital Division of the Ottawa Clinic. Beside the main switchboard, each location has its own number thus permitting direct outside dialing. In addition it can be used for area paging and as an intercom.

Preparations for installation of a computer system continue. Basic forms containing data to be fed into the computer are being completed.

The TP-11 treatment planning unit has been upgraded to a Theraplan allowing direct interface to CT patient data on magnetic tape.

Two Selectron units for remote control afterloading of intracavitary Cesium 137 sources have been delivered to the clinic.

Day care is now available in the lodge for Ottawa patients who are on treatment, either radiotherapy or chemotherapy, and who would benefit from day care. They are given emotional and social support, instruction on pain management, and are assessed as to their need to be referred to another service.

Dr. Saul Rosenberg, Professor of Medicine at Stanford University, was the first Harold Vail Visiting Professor. On December 16, 1981, he gave a formal presentation at medical grand rounds at the Ottawa Civic Hospital and a similar presentation on December 17 at the Ottawa General Hospital. The titles of his presentations were: "Non-Hodgkin's Lymphoma – Classification, Prognosis and Treatment"; and "Hodgkin's Disease – Increasing Role of Multimodality Therapy".

Dr. Ervin Epstein Sr., a dermatologist from Oakland, California, was the second Harold Vail Visiting Professor at the Division of Dermatology – Ontario Cancer Foundation, University of Ottawa, Scientific Meeting on October 22 and 23, 1982. Dr. Peter Fitzpatrick from the Princess Margaret Hospital was also a member of the panel.

A hyperthermia research group was formed to develop a co-operative research program in electromagnetically induced hyperthermia as a possible modality in treatment of cancer. Members of this group are: Prof. S.S. Stuchly of University of Ottawa, Drs. C.E. Danjoux and C. Cripps, and Messrs, L. Gerig and R. Gillies of the Ottawa Clinic.

A research program involving human tumor testing is underway in the clinic. The ultimate goal is to develop a means of determining which chemotherapeutic drugs are most likely to be effective for a particular patient.

G. E. Catton, M.B., B.S., D.M.R.T., F.R.C.P.(C)
Acting Director

ONTARIO CANCER FOUNDATION THUNDER BAY CLINIC

GENERAL HOSPITAL OF PORT ARTHUR

Director:
J. F. Kotalik, M.D.

Radiation Oncologist:
W. A. Hargan, M.D.

Clinical Assistant:
J. A. Chalykoff, M.D.

Physicist:
P. D. Sharma, M.Sc.

Business Manager:
Margaret M. Ryan

Senior Nurse:
Lorraine Bright, Reg.N.

Supervisory Radiotherapy Technician:
Janet V. Morgan, R.T.

Nurse Social Worker:
V. Marilyn Coley, Reg.N.

Senior Medical Records Officer:
Mary Pat Winfield, C.C.H.R.A.(A)

Lodge Supervisor:
Barbara C. Petty

Over the past year, the Thunder Bay Clinic has had many changes in staff.

Dr. W.A. Hargan retired as Director. He established this clinic in 1948 and served in this position for 34 years. We are all happy that Dr. Hargan remains on staff as a part-time radiation oncologist. Also, Dr. Jaclyn Duffin has resigned and has moved to Paris, France. During her two-year association with the clinic, she built a considerable practice in medical oncology, trained nurses in the administration of chemotherapy, and worked to increase co-operation with the medical schools in undergraduate and postgraduate training. An active search for two medical oncologists is underway. Vacations for our medical staff would not have been possible without the kind assistance of Dr. Lois Myers.

During the past year, for the first time, we have enrolled our patients in co-operative clinical trials of the National Cancer Institute of Canada and, after our medical staff has been completed, we hope to increase this participation.

Finally, we seem to have found a solution for our training shortage of radiotherapy technologists. The first graduate of our training program, Susan Vaillant, has just joined our staff, and two local students are enrolled in the first year of this program.

In the Medical Records Department, Mrs. Fern Adams retired as head of the department after 20 years of service. Miss Mary Pat Winfield now is in charge of this department. With the close co-operation of the Information Systems of the Foundation, we were able to carry out the various changes in the flow of information required for computerization.

In addition to our Consultative and Follow-up Clinic in Geraldton, we have started a new peripheral clinic in Fort Frances, which is located 300 km west of Thunder Bay.

Our clinical research was given a new direction when we developed a program for the computerized tomographic evaluation of lung changes after radiotherapy in co-operation with McKellar General Hospital and with the support of a grant provided by the Foundation. Increasing use of CT scanning in radiotherapy planning will be facilitated by a new planning computer. Our physics department has done an extensive study of the integration of the Selectron remote afterloading device into our system of gynocological radiotherapy. Miss Victoria Gibson, a Lakehead University student, supported by a Harold E. Johns summer studentship in medical physics, participated in this and other work of the department.

The need for a high-energy linear accelerator is increasing and a high priority for our clinic is to obtain this unit in the coming year.

J.F. Kotalik, M.D., D.M.R.T., F.R.C.P.(C)
Director

ONTARIO CANCER FOUNDATION TORONTO-BAYVIEW CLINIC

SUNNYBROOK MEDICAL CENTRE

Director:

R. D. T. Jenkin, M.B., B.S.

Radiation Oncologists:

M. P. Berry, M.B., B.S.
P. A. Catton, M.D.
R. G. MacKenzie, M.D.

Medical Oncologists:

N. Iscoe, M.D.
I. J. Kerr, M.D.
D. Osoba, M.D.
J. J. Rusthoven, M.D.
D. J. A. Sutherland, M.D.

Clinical Assistants:

H. M. Kocandrle, M.D.
T. B. McQuiston, M.D.

Physicists:

H. B. Michaels, Ph.D.
P. F. O'Brien, M.Sc.

Business Manager:

L. D. Langdon, M.H.A.

Senior Nurse:

Judy Cook, Reg.N. (to September 1982)
Catherine Johnstone, Reg.N. (from November 1982)

Senior Radiotherapy Technician:

Anne Bissett, R.T.(T)

Senior Medical Records Officer:

Micheline Mistruzzi

In December 1981, the clinic staff moved from the interim clinic to the newly completed permanent building. Thus we were well established in time for the formal opening ceremony. On May 11, 1982, Lieutenant-Governor John Aird cut the ceremonial ribbon, and the distinguished platform party included Premier William Davis and Mr. Dennis Timbrell (representing the Minister of Health Larry Grossman).

The first year in the new clinic has been one of continuing rapid growth. By the year's end we had acquired more than 60 staff members and were treating new patients at the rate of 1250 per year, almost one-half of our planned capacity.

Also this was a landmark year for the Division of Radiation Oncology. The clinic's only cobalt unit was commissioned and, within a few weeks, was operating to full capacity. By year's end our 6 MeV linear accelerator will be commissioned and will have started patient treatments. With the introduction of these two major pieces of equipment we brought the simulator and mould room "on stream". Mr. Peter O'Brien returned to Ontario from Alberta to join the Department of Clinical Physics.

The medical oncology staff increased with the appointments of Dr. Ian Kerr, who returned to Toronto following two years in pharmacology at the National Cancer Institute in Bethesda and Dr. James Rusthoven. The radiation oncology staff was strengthened by Drs. Pamela Catton and Robert MacKenzie. Dr. Terrence McQuiston joined the Division of Medical Oncology as a medical assistant. On July 1, the residency program doubled when four residents — two in medical and two in radiation oncology — started rotating through the clinic from the University of Toronto program.

The clinic staff held an Oncology Clinical Day on June 9 during which members of staff and consultants reviewed a number of common oncology problems for the practitioners in the region.

In step with these events, our associated inpatient operation — Sunnybrook Medical Centre's Department of Oncology — has increased its activity proportionally. Sunnybrook's C-wing is undergoing expansion and rebuilding so that, by 1983, we shall have new inpatient accommodation for approximately one-half of our planned 78 beds and also a new operating room.

Thus during 1982 a solid foundation has been laid for our patients service operation. Many positive events occurred and indeed the only important task remaining is to obtain adequate funding to complete the area to be occupied by our research division and to support an appropriate investigative unit.

R.D.T. Jenkin, M.B., B.S.
Director

ONTARIO CANCER FOUNDATION WINDSOR CLINIC

METROPOLITAN GENERAL HOSPITAL

Director:
J. H. Maus, M.D.

Radiation Oncologist:
G. C. K. Mok, M.D.

Medical Oncologists:
H. T. Abu-Zahra, M.B., B.Ch.
D. B. McDonald, M.D.
S. Yoshida, M.D.

Clinical Assistant:
C. Iannicello, M.D.

Physicist:
D. Smocovitis, M.Sc.

Business Manager:
Eva Schwindt

Senior Radiotherapy Technician:
Rita Macpherson, R.T.

Senior Nurses:
Amalia Beaton, Reg.N.
Mary O'Neill, Reg.N.

Senior Medical Records Officer:
Viola L. Gignac

Renovations to the Windsor Clinic were completed in 1982. These changes, by meeting most of our space requirements, greatly improved the staff's ability to meet the patients' needs. The official opening was held on February 18. Unfortunately, travel difficulties did not permit Ministry of Health representatives to come to Windsor, but the address of the Ministry's designated representative was read during the proceedings. Mrs. Mabel Krug, senior Member of the Board, cut the ribbon. During the morning, the Board of the Foundation met in the boardroom of the Metropolitan General Hospital to conduct their regular business under the chairmanship of Mr. William Wilkinson, the local representative.

On May 12, an open house was held in conjunction with Hospital Day and the Metropolitan General Hospital. In addition, many secondary school students have travelled through the clinic as part of a regularly arranged tour. A new library-conference room, which was badly needed, has proved to be most useful.

Liaison between members of the clinic staff and the Hospice of Windsor continues on a regular basis. The V.O.N., acting as our social service wing, has continued to be most valuable. Mrs. Barbara Billey, a nutritionist, gave us valued help last year and we hope it will be possible to add her to our staff. During and after their treatment, she provided much valuable advice to patients receiving radiotherapy and chemotherapy.

We continue to have vacancies for two doctors, one in medical oncology and the other in radiation oncology. Dr. Carman Iannicello has joined the medical oncology division as a clinical assistant. During his undergraduate years, Carman was an Ivan Smith Fellow here and also spent an elective period with us; thus he is familiar with the clinic and its systems of treatment. He will be with us for approximately one year.

A hard-wire linkage has been installed in the laboratory with printers at the two levels of the clinic for prompt reporting of blood counts. The turnaround time between the taking of blood and the reporting of results is now improved, particularly in our chemotherapy division.

As yet, the Windsor Clinic does not have a guaranteed number of inpatient beds. The hospital has designated 4 North Tower as the cancer floor, and is attempting to meet our needs for active treatment beds. However, the hospital is under great pressure to reduce active treatment beds and probably will lose 25 or more beds during 1982. In order to solve budgetary problems, the hospital will close a complete nursing unit during the months of December '82, January, February and March of '83.

We continue to explore the possibility of computerization of certain aspects of medical records, patient admissions and OHIP billing with the Head Office computer. Progress in this field is slow because the Ministry is short of money.

We have offered our services to the University of Windsor and St. Clair College for their career days. The latter have accepted but no date has been set.

In general, the service in Windsor continues to be busy, although the number of new patient admissions has remained relatively constant. Like other clinics in the Foundation, we look forward to new programs which will lead to improved patient services.

J.H. Maus, M.D.
Director

ONTARIO CANCER INSTITUTE

incorporating

PRINCESS MARGARET HOSPITAL

Director:

R. S. Bush, M.D.

Medical Oncology (Clinical and Research):

Ruth E. Alison, M.D.
D. E. Bergsagel, M.D.
N. F. Boyd, M.B., B.S.
J. E. Curtis, M.D.
C. Erlichman, M.D.
R. Feld, M.D.
S. Fine, M.D.
R. Hasselback, M.D., C.M.
H. A. Messner, M.D.
M. D. Minden, M.D.
I. C. Quirt, M.D.
Daniele Perrault, M.D.
J. F. G. Sturgeon, M.B., B.S.
I. F. Tannock, M.D.

Radiation Oncology (Clinical and Research):

F. A. Beale, M.B., Ch.B.
Helen A. Bean, M.D.
R. M. Clark, M.B., B.S.
B. J. Cummings, M.B., Ch.B.
A. J. Dembo, M.B., B.Ch.
P. J. Fitzpatrick, M.B., B.S.
P. G. Garrett, M.D.
Mary K. Gospodarowicz, M.D.
Moira A. Gribbin, M.B., B.S.
A. R. Harwood, M.B., Ch.B.
N. V. Hawkins, M.B., B.S.
J. G. Herman, M.D.
T. J. Keane, M.B., B.Ch.
D. G. Payne, M.D.
J. F. Pringle, M.B., Ch.B.
Gail A. Rawlings, M.D.
W. D. Rider, M.B., Ch.B.
W. J. Simpson, M.D.
S. B. Sutcliffe, M.B., M.D.
Gillian M. Thomas, M.D.

Diagnostic Radiology:

R. Blend, M.B., B.S.
S. Herman, M.D.
I. F. Majesky, M.D.
P. Y. Poon, M.B., B.S.
D. F. Rideout, M.B., B.S.

Nuclear Medicine:

Günes N. Ege, M.D.
J. L. Yeoh, M.D.

Pathology:

T. C. Brown, M.D.
J. S. Carruthers, M.D.
V. L. Fornasier, M.D.
G. J. Laroye, M.D.
Marjorie E. Platts, M.D.
Tamara Treger, M.D.

Microbiology:

P. G. Tuffnell, M.D.

Physics (Clinical and Research):

M. C. Archer, Ph.D.
M. J. Bronskill, Ph.D.
J. R. Cunningham, Ph.D.
G. DeBoer, Ph.D.
S. Foster, Ph.D.
D. M. Galbraith, B.Sc.
M. Henkelman, Ph.D.
R. P. Hill, Ph.D.
J. W. Hunt, Ph.D.
B. Japp, B.Sc.
P. M. K. Leung, Ph.D.
H. Maharaj, B.Sc.
F. P. Ottensmeyer, Ph.D.
A. M. Rauth, Ph.D.
A. J. Rawlinson, M.Sc.
W. B. Taylor, B.Eng.
J. Van Dyk, M.Sc.
H. P. Webb, C.E.T.
G. F. Whitmore, Ph.D.

Biological Research:

A. Bernstein, Ph.D.
R. Buick, Ph.D.
A. Ciampi, Ph.D.
A. J. Cunningham, Ph.D.
R. M. Gorczynski, Ph.D.
A.F. Howatson, Ph.D.
N. Hozumi, Ph.D.
V. Ling, Ph.D.
T. W. Mak, Ph.D.
E. A. McCulloch, M.D.
R. G. Miller, Ph.D.
R. A. Phillips, Ph.D.
G. B. Price, Ph.D.
C. P. Stanners, Ph.D.
J. E. Till, Ph.D.

Administrator:

Johanne E. Ratz

Assistant Administrators:

T. Brazier
T. J. D. West
W. Wilkinson

Director of Nursing:

J. Patricia Holder, Reg.N.

Senior Medical Records Officer:

I. Jean Base, R.R.L.

Librarian:

Carol Morrison, B.A., M.L.S.

The past year has seen a number of changes in the staff, and in the physical structure of the Institute. Dr. James Till stepped down as Head of the Division of Biological Research in order to pursue his research interests, chiefly in aspects of health status such as the definition and measurement of quality of life during illness. Dr. Robert Phillips was appointed Chairman of the Department of Medical Biophysics at the University of Toronto. The clinical staff was augmented by the appointments of Drs. Peter Garrett, Gail Rawlings and Simon Sutcliffe to the Department of Radiation Oncology.

The Institute was honored by a visit from Her Royal Highness, The Princess Margaret. She toured areas of the hospital which had undergone considerable change since her last visit in 1967; these included one of the newer nursing units and the CT scanning and ultrasound suites. After the tour, Her Royal Highness spoke to patients and volunteers at the Lodge before leaving.

Many structural changes have been made to help the hospital to improve service to the more than 7000 new patients seen each year, and to the increasing number of patients seen for continuing treatment and follow-up. Renovations to the area previously used as the children's ward have created additional space for the outpatient department. Four new general clinic areas have been opened, employing a design, which allows much greater flexibility of use, with adequate room for consultation and teaching, which does not interfere with the movement of patients. Special facilities are now available for ophthalmology and dental clinics. Adjacent to these is an expanded and attractively decorated day care clinic, which has improved facilities for outpatient blood transfusion and chemotherapy administration. Transfer of the cell separator to the same area has created space for an additional isolation area on the nursing unit used for bone-marrow transplantation. The opening of the new

outpatient clinics has in turn allowed much needed renovation to proceed in the original outpatient department.

Construction of a new area in the hospital for a 20 MeV linear accelerator was also completed, and at the same time the front entrance to the hospital was modified to permit easier access. Other changes are underway in the Department of Radiotherapy to replace obsolete equipment.

Education has continued to be a major responsibility at all levels within the Institute. A formal training program has been established for postdoctoral fellows, with funds provided from the Terry Fox Marathon of Hope, through the National Cancer Institute of Canada. This program will aim to attract physicians who wish to train in cancer research, and will also support a small number of Ph.D. students.

The postgraduate training program in clinical oncology continues to attract well-qualified residents, who wish to specialize in radiation oncology and medical oncology. During this year there were 18 residents in radiation oncology and 9 in medical oncology. Five trainees were successful in passing the Royal College examinations in radiation oncology. One trainee in the Department of Medicine was successful in the Royal College examinations in internal medicine, and four trainees passed the American Board examination in medical oncology.

Unfortunately few undergraduate students seek electives in oncology at the present time. The case for increased teaching in this area has again been pressed to the curriculum committee of the Faculty of Medicine, and we hope that this situation soon will improve.

Six students completed the training program for therapeutic radiographers this year and passed the examination of the Canadian Association of Medical Radiation Technologists. A successful program was organized for the postgraduate education of radiation technologists.

The Department of Nursing continued to provide educational facilities for diploma students from the community colleges, students from the University of Toronto in the B.Sc.N. program, students from Ryerson's nursing degree program in applied arts for diploma graduates, and for graduate students. Members of the department played a major role in designing and teaching a course in Cancer Nursing at Ryerson Polytechnical Institute; this course has attracted a large number of nurses from teaching and community hospitals, who wish to broaden their knowledge of the care of patients with malignant disease.

Clinical research at the Institute continues to emphasize the need for clinical trials in many disease sites. Studies in the postoperative adjuvant treatment of lung cancer involves participation in the Lung Cancer Study Group of the National Cancer Institute. Patients with bone-marrow involvement by lymphomas of poor histology have been entered in a trial co-ordinated by the National Cancer Institute of Canada. Some of the other trials conducted within the hospital have included patients with breast cancer, head and neck cancer, colorectal and stomach cancer, and ovarian and cervical cancer. Phase I studies of misonidazole, which have been completed in the hypoxic-cell, radiation-sensitizer program in cervical cancer, have

established the maximum dose of the drug, which can be safely administered with radiation. A randomized trial has started in patients with locally advanced cervical cancer to determine whether the addition of misonidazole to conventional radiation will achieve better local control and higher cure rates.

The basic research programs involve a broad range of subjects. In molecular genetics, study continues into oncogenes, and the steps involved in the development of immune response. In tumor-cell biology, new cell culture techniques are being used to study the stem cells in human ovarian cancer. In experimental chemotherapy, mammalian cells in culture, tumor spheroids and experimental tumors are being used to study the response of aerobic and hypoxic cells to a variety of agents. Research is also continuing into medical-decision making, attempting to develop and apply analytic methods to decisions used in clinical medicine.

In the area of diagnostic imaging, a new ultrasound breast scanner is undergoing clinical evaluation, studies to improve quality and to reduce exposure in diagnostic radiology are ongoing, and a new program has just begun in nuclear magnetic resonance imaging.

Finally, although a number of important visitors came to the Institute throughout the year, special mention should be made of the 20th anniversary of the development (by Drs. Till and McCulloch) of a method to measure hemopoietic stem cells. The Institute and the National Cancer Institute of Canada organized a successful symposium entitled "Cellular and Molecular Biology of Hemopoietic Stem Cell Differentiation" to mark this major occasion.

J.F.G. Sturgeon, M.B., B.S., F.R.C.P.(C)
Medical Oncologist

CONSULTATIVE AND FOLLOW-UP CLINICS

The distribution of these clinics reflects the general zones of service of the Foundation's Regional Treatment Centres in Hamilton, Kingston, London, Ottawa, Thunder Bay and Windsor; and of the Princess Margaret Hospital, Toronto.

HAMILTON

Brantford	— St. Joseph's Hospital
Guelph	— Guelph General Hospital
St. Catharines	— St. Catharines General Hospital
Welland	— Welland County General Hospital

KINGSTON

Cornwall	— Cornwall General Hospital and Hotel Dieu Hospital
Trenton	— Trenton Memorial Hospital

LONDON

Cambridge (Galt)	— Cambridge Memorial Hospital
Chatham	— Public General Hospital
Kitchener	— Kitchener-Waterloo Hospital
London	— Westminster Hospital
Owen Sound	— General and Marine Hospital
Sarnia	— St. Joseph's Hospital and Sarnia General Hospital
Stratford	— Stratford General Hospital
Wingham	— Wingham General Hospital
Woodstock	— Woodstock General Hospital

OTTAWA

Cornwall	— Cornwall General Hospital and Hotel Dieu Hospital
Pembroke	— Pembroke Civic Hospital

THUNDER BAY

Geraldton	— Geraldton District Hospital

TORONTO

North Bay	— North Bay Civic Hospital
Owen Sound	— General and Marine Hospital
Peterborough	— St. Joseph's Hospital
Sault Ste. Marie	— Plummer Memorial Public Hospital
Sudbury	— Laurentian Hospital
Timmins	— St. Mary's Hospital

WINDSOR

Leamington	— Leamington District Memorial Hospital

CLINICAL CONSULTANTS
AT ONTARIO CANCER FOUNDATION CLINICS
AND THE PRINCESS MARGARET HOSPITAL

(As at December 31, 1982)

OCF Hamilton Clinic:

M. Ali, M.D.
S. Archibald, M.D.
H. W. Beattie, M.D.
A. M. Benger, M.D.
W. F. Bennett, M.D.
B. Clark, M.D.
D. Clark, M.D.
I. R. Davis, M.D.
P. B. Dent, M.D.
A. D. DePetrillo, M.D.
J. D. Gowing, M.B., B.S.
R. A. Hadden, M.D.
D. A. Hitch, M.D.
G. K. Ingham, M.D.
B. S. Jackson, M.D.
J. Kearns, M.D.
P. Knight, M.B., Ch.B.
G. A. Lane, M.D.
J. E. McBride, M.B., Ch.B.
S. E. O'Brien, M.D.
G. O'Connell, M.D.
W. L. Orovan, M.D.
J. T. Roberts, M.B., Ch.B.
G. K. Thorsen, M.D.
B. Trossman, M.D.
W. E. C. Wilson, M.D.
C. Woolever, M.D.
J. E. M. Young, M.D.

OCF Kingston Clinic:

J. M. Blakeman, M.D.
J. A. Carmichael, M.D.
W. E. N. Corbett, M.D.
D. Dexter, M.D.
P. R. Galbraith, M.D.
A. D. Ginsburg, M.B., Ch.B.
S. F. Hall, M.D.
J. W. Kerr, M.D.
G. F. Kipkie, M.D.
K. W. Mackie, M.D.
J. R. McCorriston, M.D.
R. J. Riopelle, M.D.
D. M. Robertson, M.D.
H. D. Steele, M.D.
E. E. Sterns, M.D.
K. Taguchi, M.D.
D. M. L. Williams, M.D.

OCF London Clinic:

H. H. Allen, M.D.
W. B. Barton, M.D.
J. Coles, M.D.
G. G. Copeland, M.D.
G. DeRose, M.D.
L. L. DeVeber, M.D.
J. Duff, M.D.
C. A. Dyson, M.D.
N. J. England, M.D.
C. F. S. Fisher, M.D.
H. Goldberg, D.D.S.
R. E. Greenway, M.D.
P. J. Gullane, M.B., B.Ch.
H. Heeneman, M.D.
D. W. B. Johnston, M.D.
D. A. MacKenzie, M.D.

R. M. McFarlane, M.D.
T. D. McLarty, M.D.
E. R. Plunkett, M.D.
L. Reese, M.D.
I. D. F. Schofield, D.D.S.
M. Smout, M.D.
W. K. Stavraky, M.D.
C. A. Thompson, M.D.
J. H. Walker, M.D.
J. Wyatt, M.D.

OCF Ottawa Clinic:

R. P. Abele, M.D.
D. J. Addison, M.B., Ch.B.
G. Armstrong, M.D.
E. A. Atack, M.D.
J. W. Atkinson, M.D.
G. G. Barber, M.D.
R. Barr, M.B., Ch.B.
P. T. Barron, M.B., Ch.B.
P. Beaudry, M.D.
R. Belanger, M.D.
M. Bell, M.D.
M. E. A. Bell, M.D.
B. Benoit, M.D.
P. Benoit, M.D.
J. M. Beresford, M.B., Ch.B.
J. Bormanis, M.D.
R. Boutin, M.D.
M. Brazeau, M.D.
P. Capello, M.D.
C. C. Carruthers, M.D.
C. K. Chew, M.D.
G. C. Cimone, D.M.D.
J. C. Clark, M.D.
J. Collins, M.D.
G. G. Copestake, L.R.C.P. (U.K.)
A. Crepeau, M.D.
H. Curry, M.D.
I. Dardick, M.D.
Y. de la Bastide, L.R.C.P. (U.K.)
J. J. Deneault, M.D.
J. P. Des Groseilliers, M.D.
J. E. Devitt, M.D.
C. Don, M.B., B.S.
J. Drouin, M.D.
P. Drouin, M.D.
C. Ellis, M.D.
R. J. Fairfull-Smith, M.B., Ch.B.
J. F. Fielding, M.D.
J. B. Freeman, M.D.
S. J. Fremeth, D.D.S.
N. G. Futter, M.D.
E. Gear, M.D.
J. Gerin-Lajoie, M.D.
A. Giachino, M.D.
R. R. Gillies, M.D.
Z. Grahovac, M.D.
D. Grimes, M.D.
A. Guberman, M.D.
J. J. Hadju, D.D.S.
A. Haq, M.D.
J. Hardie, B.D.S.
I. Hart, M.B., Ch.B.
J. Henderson, M.B., Ch.B.
R. Heringer, M.D.
C. Hetenyi, M.D.
D. P. Hill, M.D.
D. Hooper, M.D.
E. Hsu, M.D.
L. B. Huebsch, M.D.
H. Hugenholtz, M.D.
G. Hurteau, M.D.
A. H. Irvine, M.D.
R. Jackson, M.D.
T. G. Jones, M.B., B.S.
N. Kanigsberg, M.D.
S. P. Kucey, D.D.S.
K. Kuwayti, M.D.
B. Lach, M.D.
G. Laframboise, M.D.
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B. Leonard, M.D.
E. Liepa, M.D.

J. B. Lightford, D.D.S.
B. Luke, M.D.
D. D. Macfie, M.B., Ch.B.
J. P. MacLeod, M.D.
N. Mayer, M.D.
W. T. E. McCaughey, M.B., Ch.B.
W. M. McIntyre, M.D.
D. E. McKay, M.D.
N. V. McPhail, M.D.
S. Meban, M.B., Ch.B.
S. Mercer, M.D.
N. Z. Mikhael, M.D.
D. Moors, M.D.
B. Morton, M.D.
J. E. Mullens, M.D.
R. Nelson, M.D.
P. F. Odell, M.D.
H. Oxorn, M.D.
R. J. Patterson, M.D.
A. Peloquin, M.D.
E. W. Peterson, M.D.
D. N. Preston, M.D.
M. T. Richard, M.D.
R. N. Rivington, M.D.
J. Robblee, M.D.
N. A. Russell, M.D.
H. J. Sachs, M.D.
G. J. Sarwer-Foner, M.D.
G. Sauve, M.D.
A. C. Scott, M.D.
S. Y. Shirley, M.D.
M. Silverman, M.D.
D. S. Skene, M.D.
R. K. Smiley, M.D.
H. Tao, M.D.
J. R. Taylor, M.D.
W. G. Thompson, M.D.
M. Tousignant, M.D.
G. N. W. Tse, M.D.
H. K. Uhthoff, M.D.
F. W. Vaillancourt, M.D.
J. H. Walters, M.D.
H. Warnes, M.D.
A. G. Watson, M.D.
C. Watters, M.D.
D. S. Whittingham, M.D.

OCF Toronto-Bayview Clinic:

D. Assaad, M.D.
B. D. Birt, M.B., B.S.
D. H. Cowan, M.D.
G. M. Davies, M.B., B.Ch.
J. L. Freeman, M.D.
L. From, M.D.
J. S. Gruss, M.B., B.Ch.
S. Hanna, M.B., B.Ch.
A. W. Harrison, M.D.
J. H. P. Main, B.D.S.
H. A. B. Miller, M.B., B.S.
J. S. Senn, M.D.
G. A. Taylor, M.D.
P. M. Webster, M.D.

The Princess Margaret Hospital, Toronto:

U. Ambus, M.D.
A. G. Andrews, D.D.S.
H. W. Bain, M.D.
M. A. Baker, M.D.
J. L. M. Bean, M.D.
M. Berry, M.D.
N. Bharatwal, M.D.
B. D. Birt, M.B., B.S.
M. E. Blackstein, M.D.
T. D. R. Briant, M.D.
D. P. Bryce, M.D.
M. B. Buckspan, M.D.
M. L. Bunker, M.D.
G. N. Burrow, M.D.
J. J. Caesar, M.D.
D. H. Carver, M.D.
H. S. L. Chan, M.B.
A. W. Chisholm, M.D.
R. H. Comisarow, M.D.
A. W. Conn, M.D.
J. G. Connolly, M.D.

J. D. Cooper, M.D.
D. H. Cowan, M.D.
J. S. Crawford, M.D.
L. G. Douglas, M.D.
W. M. Easterbrook, M.D.
R. J. Evans, M.D.
W. K. Evans, M.D.
R. E. Falk, M.D.
E. Farber, M.D.
R. M. Filler, M.D.
E. B. Fish, M.D.
B. K. Fisher, M.D.
M. M. Fisher, M.D.
A. E. Franklin, Ph.D.
J. M. Fredrickson, M.D.
J. L. Freeman, M.D.
B. L. Gallie, M.D.
W. O. Geisler, M.D.
A. H. Gerulath, M.D.
R. J. Ginsberg, M.D.
C. M. Godfrey, M.D.
M. Goldberg, M.D.
D. A. Gordon, M.D.
B. J. Green, M.B. Ch.B.
G. Haber, M.D.
J. A. Hakes, M.B., Ch.B.
M. L. Halperin, M.D.
J. L. Harkins, M.D.
L. R. Harnick, M.D.
G. D. Hart, M.D.
D. E. Hastings, M.D.
R. E. Hayden, M.D.
R. I. Hector, M.D.
C. Hegarty, M.B., B.Ch.
R. C. Hicks, M.B., B.S.
M. E. Hill, M.D.
M. S. Hill, L.R.C.P.
C. H. Hollenberg, M.D.
R. B. Holmes, M.D.
N. S. Hradsky, M.D.
R. C. Hunter, M.D.
M. A. Hutcheon, M.D.
R. D. T. Jenkin, M.B., B.S.
M. Jewett, M.D.
A. T. Jousse, M.D.
A. S. Katz, M.D.
A. Keresteci, M.D.
W. K. Kerr, M.D.
M. H. King, M.D.
G. H. Knutson, M.D.
B. Langer, M.D.
F. Langer, M.D.
E. L. Lansdown, M.D.
V. G. Lawson, M.D.
W. D. Leers, M.D.
G. M. Lickrish, M.B., Ch.B.
K. E. Livingston, M.D.
F. H. Lowy, M.D.
W. J. C. MacArthur, M.D.
R. D. MacDonald, M.D.
I. M. MacKay, M.D.
T. A. MacKenzie, M.D.
I. Macnab, M.B., Ch.B.
L. J. Mahoney, M.D.
N. E. Marcon, M.D.
P. H. McCleary, M.D.
P. D. McClure, M.D.
J. S. McGrail, M.D.
J. W. Meakin, M.D.
R. I. Mitchell, M.D.
T. J. Molony, M.B.
T. P. Morley, B.M., B.Ch.
T. M. Murray, M.D.
R. A. Mustard, M.D.
R. E. Myers, M.D.
J. R. Nethercott, M.D.
R. J. Osborne, M.D.
D. Osoba, M.D.
J. A. Palmer, M.D.
F. R. Papsin, M.D.
F. G. Pearson, M.D.
R. G. Perrin, M.D.
K. Pritchard, M.D.
P. Ramachandran, M.D.

C. A. Ramsay, M.D.
J. T. Rankin, D.M.
I. B. Rosen, M.D.
R. K. Schachter, M.D.
J. Schatzker, M.D.
A. A. Scott, M.D.
M. Scott, M.D.
J. S. Senn, M.D.
M. Silberfeld, M.D.
G. Foster Smith, M.D.
H. S. Smyth, M.D.
H. A. Smythe, M.D.
M. J. Sonley, M.D.
M. L. Soots, M.D.
A. H. Squires, M.D.
M. Stancer, D.D.S.
R. M. Stone, M.D.
D. J. Sutherland, M.D.
J. M. Symington, B.D.S.
G. A. Thompson, M.D.
S. A. P. Tindal, M.B., Ch.B.
M. L. S. Vachon, Ph.D.
C. P. Vernon, M.D.
R. Volpe, M.D.
C. P. N. Watson, M.D.
N. A. Watters, M.D.
G. D. Webb, M.D.
R. H. Wilkinson, M.D.
C. C. Williams, M.D.
Donald R. Wilson, M.D.
Douglas R. Wilson, M.D.
F. R. H. Wrigley, M.B., B.S.
A. Zipursky, M.D.
R. M. Zuker, M.D.

SPECIAL SERVICES

PROVISION OF SPECIAL DRUGS TO TREAT MALIGNANT DISEASE

The Foundation provides special chemotherapeutic agents to cancer patients who are residents of Ontario and are at home under the care of their doctors. This program was undertaken to assist those patients who find the cost of prolonged therapy with expensive drugs beyond their financial resources. In 1981, the drug service provided medications for 1572 patients.

As the number of Ontario residents covered by prescription drug insurance plans (including the Ontario Drug Benefit Plan) continues to rise, the number of patients served by the Foundation's drug service has been decreasing, although in 1981 the number of prescriptions increased by 4% (Table I).

TABLE I

Patients Served and Prescription Volume 1972-1981

Year	Patients			Prescriptions
	New*	Old**	Total	
1972	1,707	1,524	3,231	14,659
1973	1,827	1,645	3,472	16,484
1974	1,974	1,909	3,883	17,119
1975	1,868	1,811	3,679	16,771
1976	1,722	1,499	3,221	14,702
1977	1,225	1,147	2,372	12,501
1978	1,113	1,108	2,221	12,183
1979	846	911	1,757	10,312
1980	775	860	1,635	9,398
1981	771	801	1,572	9,803

*A "new" patient is one who has received drugs for the first time ever.
**An "old" patient is one who previously was registered in the drug service.

The total cost of the drug service in 1981 was $307,676.97 — an increase of 16% from the $265,059.36 in the previous year (Table II). The cost per patient has increased to $195.72 in 1981 from $162.12 in 1980. The cost per prescription has increased to $31.36 in 1981 from $27.83 in 1980.

TABLE II

Cost of Drug Service
1972-1981

Year	Payments for Drugs	Total Cost of Drug Service
1972	150,514.82	153,961.68
1973	182,210.56	185,756.15
1974	206,189.41	208,541.66
1975	214,942.30	216,055.35
1976	175,949.99	177,984.37
1977	148,418.40	152,021.06
1978	209,817.12	210,836.18
1979	257,136.92	261,512.36
1980	259,973.32	265,059.36
1981	307,376.30	307,676.97

In order of frequency, the principal sites (Table III) treated through the Foundation's drug service in 1981 were: breast — 42%; leukemia — 12%; and Hodgkin's disease — 3%. The increasing use of many new costly therapeutic agents, particularly in the treatment of breast cancer, has contributed to the increasing cost of the drug service.

TABLE III

Number of Patients Served by Major Site of Cancer

1972-1981

Year	Breast	Leukemia	Prostate	Hodgkin's Disease	Ovary	Body of Uterus	Other	Total Patients
1972	560	458	645	150	127	66	1,225	3,231
1973	763	658	649	160	125	70	1,047	3,472
1974	667	457	753	162	161	51	1,632	3,883
1975	664	491	571	146	189	85	1,533	3,679
1976	863	423	264	128	196	56	1,291	3,221
1977	712	335	72	91	140	41	981	2,372
1978	741	300	51	92	144	46	847	2,221
1979	598	256	42	72	93	47	649	1,757
1980	656	225	23	49	64	35	583	1,635
1981	667	185	20	49	48	26	577	1,572

CARCINOEMBRYONIC ANTIGEN (CEA) AND STEROID-RECEPTOR ASSAYS PROGRAM

The Ontario Cancer Treatment and Research Foundation is administering and monitoring a program for carcinoembryonic antigen (CEA) and steroid-receptor assays which is funded by the Ministry of Health. The CEA assays for *confirmed* cases of cancer and the steroid-receptor assays for *confirmed* cases of breast carcinoma are available, at no charge, to a patient when these assays are performed in the designated laboratories listed below.

During the fiscal period April 1, 1981 to March 31, 1982, 3384 steroid-receptor assays and 21,550 CEA assays have been performed in the designated laboratories.

All laboratories in Ontario are familiar with the program and can provide the details of the data required, sample requirements and specimen transportation. Specimens can be referred to the participating laboratories listed below either directly or through the laboratory which usually provides such services.

Laboratories in the CEA-Assay Program

McMaster University Medical Centre,
1200 Main Street West,
Hamilton, Ontario L8S 4J9 tel: (416) 525-9140
Dr. E. D. Ryan

Kingston General Hospital,
Stuart Street,
Kingston, Ontario L7L 2V7 tel: (613) 547-2121
Dr. A. F. Clark

Victoria Hospital,
375 South Street,
London, Ontario N6A 4G5 tel: (519) 432-5241
Dr. E. R. Tustanoff

Ottawa Civic Hospital,
1053 Carling Avenue,
Ottawa, Ontario K1Y 4E9 tel: (613) 729-2511
Dr. C. Lapkoff

General Hospital of Port Arthur,
460 North Court Street,
Thunder Bay, Ontario P7A 4X6 tel: (807) 344-6621
Dr. F. J. Lone

Sunnybrook Medical Centre,
2075 Bayview Avenue,
Toronto, Ontario M4N 3M5 tel: (416) 486-3626
Dr. A. Malkin

Laboratories in the Steroid-Receptor-Assay Program

McMaster University Medical Centre, — Dr. E. D. Ryan
1200 Main Street W.,
Hamilton, Ontario L8S 4J9 tel: (416) 525-9140

Kingston General Hospital, — Dr. A. F. Clark
Stuart Street,
Kingston, Ontario K7L 2V7 tel: (613) 547-2121

Victoria Hospital, — Dr. E. R. Tustanoff
375 South Street,
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DIAGNOSTIC BIOPSY SERVICE AND VOLUNTARY REPORTING BY PATHOLOGISTS

The diagnostic biopsy service was established by the Foundation to pay for biopsies on uninsured patients. In 1981, 3690 specimens were submitted by dentists (4172 in 1980). Thirty-two of these biopsies were malignant.

The number of reports voluntarily submitted by the directors of pathology departments has continued to increase and, in 1981, 39,000 reports were submitted, an 8% increase over the 36,088 reports submitted in 1980.

Table I presents the distribution of biopsy and surgical pathology reports received by the Foundation during 1980 by primary site of the malignant neoplasms reported; data on reports for previous years are included for comparison. These reports are used in the generation of cancer incidence data for Ontario and are most valuable in confirming the diagnosis of new cases. The Cancer Act, R.S.O. 1980, Chapter 57, Section 4, Item 7, provides protection for physicians, dentists and hospitals reporting information on cancer incidence to the Foundation. The information from the reports is used for epidemiological and statistical purposes only.

The Foundation gratefully acknowledges the continuing co-operation of the participating pathologists and hospitals, and the support of the Ontario Association of Pathologists in the acquisition of these data.

TABLE I

Malignant Biopsy Reports and Surgical Pathology Reports by Site

1976-1980

SITE OF PRIMARY	1976		1977		1978		1979**		1980**	
	Biopsies	Surgical*	Biopsies	Surgical*	Biopsies	Surgical*	Biopsies	Surgical*	Biopsies	Surgical*
Lip	14	90	9	102	13	158	13	157	10	186
Tongue	13	96	7	86	10	145	11	152	14	179
Rest of mouth	31	177	22	174	32	242	30	267	41	315
Pharynx, tonsil	10	118	7	157	11	177	5	200	4	241
Rectum, anal canal	6	955	1	961	10	1,451	20	1,559	26	1,870
Other digestive	2	2,239	2	2,331	5	3,852	3	3,884	5	4,853
Nose, middle ear, sinus	—	39	1	39	1	56	1	44	—	56
Larynx	—	240	1	235	—	303	1	322	—	435
Lung, bronchus, trachea	5	977	2	1,131	—	1,807	4	1,747	4	2,247
Breast	21	2,094	25	1,921	26	3,314	13	3,436	9	3,167
Cervix uteri, *in situ*	—	775	—	784	1	1,058	—	1,122	—	1,581
Cervic uteri, invasive	5	304	7	338	8	482	9	483	6	536
Corpus uteri	—	761	772	771	5	1,127	1	1,142	—	1,337
Other female genital organs	7	379	17	455	5	717	4	593	7	691
Male genital organs	1	1,088	—	1,192	—	1,946	2	1,760	—	2,460
Urinary organs	5	1,442	—	1,481	—	2,600	—	2,488	1	3,038
Skin, all types	690	1,208	771	975	759	1,808	1,057	5,454	585	7,615
Malignant melanoma	(10)	(337)	(9)	(378)	(8)	(687)	(19)	(679)	(4)	(751)
Squamous-cell carcinoma	(175)	(400)	(194)	(455)	(154)	(903)	(162)	(1,109)	(115)	(1,354)
Basal-cell carcinoma	(500)	(290)	(563)	(—)	(589)	(—)	(872)	(3,581)	(464)	(5,422)
Other or unstated	(5)	(181)	(5)	(152)	(8)	(218)	(4)	(85)	(2)	(88)
Brain, nervous system	—	141	—	167	1	244	—	190	—	278
Bone	3	62	—	63	—	88	1	67	—	80
Lymphatic and hemopoietic tissues	15	613	12	698	9	1,031	14	1,269	20	2,171
Other sites	4	1,405	9	1,143	8	1,707	5	2,735	4	2,752
TOTAL	832	15,203	895	15,207	904	24,313	1,194	29,070	736	36,088

*Surgical pathology reports submitted voluntarily by hospitals not usually reporting through cancer clinics or registries.

**Does not include additional reports of carcinoma *in situ* of other sites and of neoplasms of uncertain behavior.

SPERM BANKING

Sperm banking refers to the process of freezing, low temperature storage and subsequent thawing of ejaculated semen to provide viable spermatozoa for fertilization. It is a useful technique before potentially sterilizing therapy for malignancy. Radiotherapy and chemotherapy temporarily or permanently impair spermatogenesis in many cases. A number of pelvic and retroperitoneal surgical procedures can impair erection and/or ejaculation. Parasympathetic nerve injury may result in loss of erection and sympathectomy can eliminate seminal emission into the urethra before ejaculation. These effects may also be permanent.

Post-treatment infertility is becoming more common as treatment of malignancy in men in their reproductive years improves survival. Therefore we anticipate that more men will ask for pretreatment sperm banking. Unfortunately, pretreatment semen quality is not always sufficient for banking. Sperm counts may be deficient particularly with testicular tumors; approximately 40% of these patients have marked suppression but the remaining 60% follow a normal distribution. These effects are less marked in non-germinal malignancies, e.g. Hodgkin's disease and non-Hodgkin's lymphoma. If the count is less than $40x10^6$/ml with motility of less than 40%, the process of freezing frequently produces a high rate of cell death precluding banking. In this situation unrelated donor semen may be banked for artificial insemination.

The success of banking depends on mixing fresh semen with a cryopreservative before freezing and storage. Once in liquid nitrogen (-196°C) semen may be stored for long periods. Insemination has been successful using thawed semen that was stored for more than 10 years. Overall, pregnancy rates of approximately 60% have been reported using frozen semen. It is essential that as much semen as possible be stored before treatment to maximize the opportunity for conception. There is no evidence that sperm banking induces significant genetic change. There is considerable individual variation during freezing so that on occasion even normal-looking semen may not freeze well. Test freezing is therefore essential before making a decision to go ahead.

At present there are no commercial sperm banks in Canada. A sperm bank for cancer patients at the Wellesley Hospital in Toronto (416-966-6910) is funded by the Ontario Cancer Treatment and Research Foundation. Arrangements can be made directly or through Dr. Michael Jewett (416-966-7804). A fresh ejaculate must be analyzed and assessed for its ability to freeze and thaw. A minimum of 3-4 ejaculates are then collected with a minimum of two days abstinence between specimens. This collection can be co-ordinated with the work up of the patient and need not postpone therapy. If local facilities are available to freeze cells, they may be transported to Toronto for storage.

Before they begin treatment, physicians and surgeons who participate in cancer therapy should counsel patients about potential sterilization. Sperm banking is a potential option if the patient wishes. No charge is made to cancer patients for this service.

LODGES FOR AMBULATORY CANCER PATIENTS

At present, the Foundation administers and provides the operating costs for the six lodges for ambulatory cancer patients being seen for diagnosis or treatment at one of the regional treatment centres. Operating from facilities provided by the host hospitals or from free-standing buildings (built from funds raised by the Canadian Cancer Society, Ontario Division, from the people of Ontario and subsequently deeded to the Foundation by the Society), these lodges provide comfortable, supportive accommodation, with minimal supervision, to out-of-town cancer patients under investigation or undergoing treatment at the regional centre.

The cost of this accommodation is borne by the Foundation because regionalization of treatment requires that patients often must travel a considerable distance to the treatment centres (without these facilities, the patients would have required hospitalization at far greater expense to the Province). When beds are available in the hostels, escorts also are accommodated, at minimal cost.

The current facilities, including number of beds and patient days spent in each during the fiscal year ended March 31, 1982, are as follows:

		Number of Beds	Patient Days
HAMILTON	Hamilton Hostel	4	541
KINGSTON	Quinte-Thousand Islands Lodge	26	3,707
LONDON	Thameswood Lodge	30	7,510
OTTAWA	Maurice J. Grimes Lodge	40	6,260
THUNDER BAY	Amethyst House Lodge	18	2,560
TORONTO	Princess Margaret Hospital Lodge	105	24,020

If the necessary government approval is obtained to cover operating costs, and the Society can identify trends for construction, the Foundation plans in 1983 to build a new lodge on the grounds of the Henderson General Hospital in Hamilton to serve the Hamilton Clinic. Also it is hoped that Thameswood Lodge, which serves our London Clinic, can be expanded.

To date, patients who require hostel accommodation while being treated at the Toronto-Bayview Clinic (which opened in May 1982) have been housed in facilities offered, on a temporary arrangement, by Sunnybrook Medical Centre, or, on occasion, in the Princess Margaret Hospital Lodge.

TRANSPORTATION OF CANCER PATIENTS

The Foundation covers the cost of transportation of those patients directed to one of its treatment centres or to the Princess Margaret Hospital, who live beyond a 25-mile radius of the centre and are considered in financial need. Usually this transportation is arranged by the local unit of the Canadian Cancer Society, which subsequently is reimbursed by the Foundation.

For the fiscal year ended March 31, 1982, the total cost for transportation of patients was $323,405, compared to $233,232 for the fiscal year ended March 31, 1981.

RESEARCH PROGRAMS

SUMMARY OF OCTRF RESEARCH

As set out in the Cancer Act of 1943, the Foundation supports a research program including: i) salary support for research personnel; ii) project support; and iii) core support for the research programs at the Kingston and London Clinics and at the Ontario Cancer Institute. Funds to support these programs are provided through the annual legislative vote of the Ministry of Health, bequests and donations, and recently through special awards from the Provincial (lottery) funds.

In 1977 the Foundation received an award of $2,000,000 from the Provincial (lottery), which enabled it to maintain the various aspects of its research program for the following two or three years. The second award ($1,000,000), received in 1980 in honor of Terry Fox, became the "Terry Fox Research Fund (Ontario)" and is being used to support young career scientists in the field of cancer research; initially, in accordance with the guidelines set out by the Ministry, only the interest on the fund will be used for salary support. The third award ($500,000) was received in 1981 following the Foundation's submission to a provincial lottery competition for funds to establish a clinical trials program in oncology.

The Foundation has been most appreciative of these awards from the lottery funds. However in 1981, despite this assistance, the Foundation recognized it could not continue supporting its research program at an adequate level unless additional funding was available on an annual basis, from the legislative vote or some other source. An ad hoc committee of the Board met in April 1981 to review the mechanisms of funding cancer research in Ontario, with particular reference to the research programs of the Foundation, including priorities of programs, distribution of funds and interaction with the Government of Ontario and the National Cancer Institute of Canada. Initially the committee recommended that the Foundation communicate with the Ministry to determine whether any additional funding might be forthcoming through the legislative vote. In accordance with this recommendation, a submission was made to the Ministry in September 1981 and, in response to this request, the Chairman of the Foundation was advised that, at that time, the Ministry was not in a position to increase base budgets for any agencies.

In addition to the monetary problems facing the Foundation, it was generally agreed that additional research personnel were needed in the Foundation clinics and the health sciences complexes throughout the Province and that the ad hoc committee should consider this problem before making recommendations concerning the Foundation's research program in the future.

In light of the Ministry's response and the need for additional research personnel, after careful consideration of the availability of funds from other sources for support

of research projects, etc., the ad hoc committee recommended that the Foundation phase out its grants-in-aid program and, as funds become available from this procedure, recruit additional research personnel for the clinics and health sciences complexes. This recommendation was approved by the Board of the Foundation early in 1982.

Support of Research Personnel

In the year 1982-83, the Foundation supported three career scientists — two in the Kingston Clinic and one in the London Clinic. In addition, seven research associates were supported on a full- or part-time basis — one at McMaster University, five at the University of Toronto and one at the University of Western Ontario. Total personnel cost $437,365.

The Foundation also provides salary support for the senior scientific staff (28.5 full-time equivalents) at the Ontario Cancer Institute (approximately $1,424,850).

In accordance with the decision to recruit additional research personnel, an ad hoc committee of the research committee was struck in July 1982 to establish guidelines and terms of reference for the appointment and support of career scientists and research associates through the Foundation's general research funds or the Terry Fox Research Fund (Ontario). The recommendations of this committee will be considered by the research committee and the Board of the Foundation in early 1983.

Initially, the Foundation plans to recruit additional career scientists to the Hamilton, London and Ottawa Clinics, and as research space and/or programs are available such scientists will be appointed to other university-affiliated clinics.

The Foundation will also consider recommendations from the Deans of Medicine for the appointment of research associates in the health sciences complexes as funds permit.

In December 1982, the Foundation appointed the first scientist to be supported by the Terry Fox Research Fund (Ontario). This appointment will take effect April 1, 1983, and in addition to salary support, the Foundation will provide some "start-up" funds and, if necessary, operating funds for the initial year of the appointment.

Grants-in-Aid

In October 1981 the Foundation received 61 applications for support of research projects totalling $2,736,772. Of these, 40 were approved by the research committee and Board of the Foundation for full or partial support in an amount of $1,426,508. As in the past few years, because of the Foundation's fiscal constraints, many of the applicants applied to the National Cancer Institute of Canada and/or other granting agencies as well as to the Ontario Cancer Treatment and Research Foundation. As a result of this, seven applicants chose to accept funding from another agency, thereby reducing the number supported by the Foundation to 33 (7 new) and the amount awarded to $1,139,481 for the 1982/83 granting year.

New projects supported in 1982 were:

HAMILTON

McMaster University:

R. E. Garfield
D. Inman — Presence and regulation of gap junctions in cancerous and non-cancerous tissues

KINGSTON

Queen's University:

A. Morales — Immunochemical studies on tumors of the genito-urinary tract

THUNDER BAY

Ontario Cancer Foundation Thunder Bay Clinic:

J. F. Kotalik — Study of postradiation changes in lung using computerized tomography

TORONTO

Hospital for Sick Children:

R. Baumal, M. J. Phillips
C. Smith and H. Yeger — Intermediate filament proteins as markers in pediatric malignancies

Ontario Cancer Foundation Toronto-Bayview Clinic:

J. J. Rusthoven
D. Osoba — Killer and suppressor-cell activities in cancer

Ontario Cancer Institute:

R. N. Buick
A. Ciampi — Stem-cell model of human tumor growth

Appendix B contains a list of papers published in 1981 by research associates, career scientists, grantees and members of the Foundation staff.

As a result of the Foundation's decision to phase out the grants-in-aid program, the Foundation did not hold a grants-in-aid competition in October 1982. However nine of the projects approved in the 1982/83 competition were approved as two-year term grants and will be funded for the 1983/84 granting year in the amount of approximately $335,000.

Grantees have been advised that they may retain any balance in their grants to continue their research as long as possible.

Core Support of Research Programs

In addition to providing salary support for the senior scientific staff at the Ontario Cancer Institute, the Foundation provides core support for technicians, mechanics,

secretaries, supplies, etc. The amount awarded for 1982/83 for this purpose was approximately $515,075.

Amounts of $26,828 and $38,846 were awarded to the Kingston and London Clinics respectively, providing support for common expenses such as technicians, secretaries, service contracts, glass-washing, etc., for the 1982/83 granting year.

Ontario Clinical Oncology Group

The Foundation is most appreciative of the $500,000 awarded from the Provincial lottery funds to establish a clinical trials program in oncology through the Province of Ontario.

Dr. P. B. McCulloch of the Hamilton Clinic has been appointed program co-ordinator of the Ontario Clinical Oncology Group and the Department of Clinical Epidemiology and Biostatistics at McMaster University, under the chairmanship of Dr. Peter Tugwell, has agreed to provide the biometric base for the program.

In November 1982, Dr. McCulloch sent a call for protocols to members of the Foundation clinics, the Ontario Cancer Institute, consultants and other interested individuals throughout the province. In response to this request, several protocols have been received and will be reviewed by the policy committee in January 1983. It is anticipated that the initial trial will be activated in March or April 1983, and that further trials may follow later in the year. The number of trials will depend upon the complexity and cost of each individual trial, recognizing the financial limitation of approximately $125,000 per annum for this purpose.

Mary R. Parkes
Research Secretary

ONTARIO CANCER FOUNDATION RESEARCH ASSOCIATES IN THE HEALTH SCIENCES COMPLEX

McMASTER UNIVERSITY, HAMILTON

Sheun-Kuei Liao, Ph.D., Department of Pediatrics and Ontario Cancer Foundation Hamilton Clinic

TORONTO WESTERN HOSPITAL

Michael A. Baker, M.D.
Herbert F. Haberman, M.D.

UNIVERSITY OF TORONTO

John G. Connolly, M.D., Department of Surgery
Brenda L. Gallie, M.D., Department of Ophthalmology
G. Elizabeth Mobbs, Ph.D., Department of Surgery

UNIVERSITY OF WESTERN ONTARIO, LONDON

Kathleen M. Stavraky, M.D., Ph.D., Department of Epidemiology and Preventive Medicine

REPORTS ON RESEARCH PROJECTS

HAMILTON

McMaster University:

Serology of Human Malignant Melanoma
P. B. Dent, S. K. Liao, D. P. Singal and P. B. McCulloch

Seroepidemiologic Study of Endogenous Sex Hormones in Neoplastic Disease of the Endometrium
C. A. Woolever and B. R. Bhavnani

Absorption and Metabolism of Equine Estrogens in Normal Men and Postmenopausal Women
B. R. Bhavnani and C. A. Woolever

Chemotactic Inhibitors in Cancer
L. A. Mandell

Ontario Cancer Foundation Hamilton Clinic:
Clinical Investigations

KINGSTON

Ontario Cancer Foundation Kingston Clinic:
Clinical Investigations

Queen's University:

Regulation of Granulopoiesis in Leukemia
P. R. Galbraith

Immunochemical and Biochemical Markers in Prostatic Disease
A. W. Bruce and D. E. Mahan

Function and Augmentation of Cytotoxicity in Genitourinary Cancer
A. Morales

Natural Killer (NK) Cell Function in Human Malignant Disease: Basic and Clinical Studies
H. F. Pross

Clinical Trial of Hematoporphyrin Photoradiation Therapy for Cancer
J. C. Kennedy

LONDON

Ontario Cancer Foundation London Clinic:

Investigation of Physical Radiation Parameters
D. J. Dawson

Combined Modality Treatment of Cancer Using Multicell Spheroids and Transplanted Tumor in Mice
W. R. Inch

Additional Investigations

University of Western Ontario:

A Cohort Study of the Effect of Age at First Full-Term Birth upon the Risk of Death from Breast Cancer
K. M. Stavraky, M. E. Smith, A. E. Donner, J. R. Miller and S. H. Uh

The Effect of Socioeconomic Status on the Prognosis of Cancer of Various Sites
K. M. Stavraky and J. E. Kincade

OTTAWA

Ontario Cancer Foundation Ottawa Clinic:
Clinical Investigations

University of Ottawa:

Studies of Polyamine and Cyclic Nucleotide Metabolism in Cancerous Prostate
R. L. Singhal

THUNDER BAY

Ontario Cancer Foundation Thunder Bay Clinic:

Study of Postradiation Changes in Lung Using Computerized Tomography
J. F. Kotalik

TORONTO

Hospital for Sick Children:

Heterogeneity of Acute Lymphoblastic Leukemia of Childhood
E. W. Gelfand, H-M Dosch and M. Letarte

Simultaneous Quantitation of Methotrexate and 7-Hydroxymethotrexate by HPLC
S. J. Soldin and S. M. MacLeod

Ontario Cancer Institute incorporating the Princess Margaret Hospital:

Toxicity Study of Metronidazole: Hypoxic-Cell Radiation Sensitizer
G. M. Thomas and R. S. Bush

Prospective Study of Postoperative Therapy in Epithelial Ovarian Cancer
A. J. Dembo and J. F. G. Sturgeon

Leukemia Program at the Ontario Cancer Institute
E. A. McCulloch and J. E. Curtis

Search for Prognostic Factors in Clincally-Staged Patients with Hodgkin's Disease
D. E. Bergsagel

Mammographic Patterns as Indicators of Risk Factors for Breast Cancer
N. F. Boyd, B. O'Sullivan, J. E. Campbell, E. Fishell, I. Simor, G. Cooke and T. Germanson

Classification of Survival Curves
A. Ciampi

Clinical Trials Secretary for Gastrointestinal Tumor Group
B. J. Cummings

Evaluation of New Ultrasound Diagnostic Systems to Detect and Characterize Breast Neoplasms
J. W. Hunt, F. S. Foster and E. Fishell

Immunologic Probes of Drug Resistance in Human Tumor Cells
G. B. Price

Clinical Trials in Breast Cancer
R. M. Clark, N. F. Boyd, U. Ambus and K. I. Pritchard

Phase III Clinical Trial of Misonidazole and Radiation Therapy
G. M. Thomas, A. M. Rauth, B. J. Cummings and R. S. Bush

Toronto General Hospital:

Chromosome Studies in Retinoblastoma
H. A. Gardner

University of Toronto:

Hormonal Control of Prostatic Cancer
B. G. Mobbs

Evaluation of Screening for Carcinoma of the Cervix
E. A. Clarke and T. W. Anderson

The Irradiated Larynx and Voice
M. L. Stoicheff and J. M. Fredrickson

Research Unit of the Division of Epidemiology and Statistics of the Ontario Cancer Treatment and Research Foundation
E. A. Clarke, R. F. Spengler, C. L. Soskolne and N. Kreiger

Retinoblastoma as a Model for Tumor-Host Interactions
B. L. Gallie . . . . .

Construction and Testing of Coded-Aperture Collimation Systems for Gamma-Ray Cameras
M. L. G. Joy . . . . .

Epidemiology of Cervical Dysplasia
E. A. Clarke and G. Lickrish . . . . .

Endoscopic Photography of the Vasculature of Recurrent Superficial Bladder Tumors
J. G. Connolly . . . . .

Evaluation of an Electromechanical Larynx
V. S. Dayal and M. L. G. Joy . . . . .

Women's College Hospital:

Cohort Study of Factors Associated with the Development of Breast Cancer
K. I. Pritchard and M. Wynne-Jones . . . . .

McMaster University, Hamilton

SEROLOGY OF HUMAN MALIGNANT MELANOMA*

P. B. DENT**, S. K. LIAO†, D. P. SINGALL†† and P. B. McCULLOCH‡
Hamilton, Ontario

The objectives of this research are to determine the spectrum of antigens expressed on human melanoma cells as defined by sera from pregnant women. Many of the human tumor antigens, which have been described to date, are differentiation antigens, which normally are expressed on fetal tissues at various stages of gestation. In our previous studies, we determined that there was only a low incidence of antimelanoma antibody in sera from patients with melanoma, and that the reactivity was not restricted to melanoma cells. The most reactive sera we studied came from women who previously had borne children, and this raised the possibility that the antigens involved might be oncofetal or differentiation antigens. To date, we have screened sera from 12 multiparous females, who are known to have antibodies against histocompatibility antigens. Eleven of these patients have had high-titre reactivity against both melanoma and non-melanoma cell lines which, by appropriate absorption, could be dissociated from their anti-HLA reactivity. However, the spectrum of reactivity appears to be complex in that a number of different specificities could be defined.

We intend to pursue our examination of the antigenic specificity of sera from multiparous females in order to better define the heterogeneity of melanoma-associated antigens. In addition, it is known that women with melanoma have a better prognosis than men, and we plan to examine the possibility that oncofetal antigens or immune responses to these antigens may play a role in the outcome of this malignancy. We will determine the incidence and factors influencing sensitization to melanoma-associated

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*Project 276. (Formerly titled "Maintenance of Human Tumors in vitro for Immunologic Studies")

**Professor of Pediatrics and Pathology, McMaster University, Hamilton; and Consulting Immunologist, Ontario Cancer Foundation Hamilton Clinic.

†Associate Professor of Pathology and Pediatrics, McMaster University; and Ontario Cancer Foundation Research Associate, Ontario Cancer Foundation Hamilton Clinic.

††Professor of Pathology, McMaster University.

‡Medical Oncologist, Ontario Cancer Foundation Hamilton Clinic; and Associate Professor of Medicine, McMaster University.

antigens in pregnant women, and establish the degree of heterogeneity of the antigenic determinants involved in this response. If it is possible to define a finite number of specificities, we will look for clinical correlates of the presence of certain antigens on tumors in vivo. We also plan to characterize the antigens involved with a view to define tumor markers, which could be used in the management of patients with malignant melanoma.

SEREOPIDEMIOLOGIC STUDY OF ENDOGENOUS SEX HORMONES IN NEOPLASTIC DISEASE OF THE ENDOMETRIUM*

C. A. WOOLEVER** and B. R. BHAVNANI†, *Hamilton, Ontario*

Cancer of the lining of the uterus (the endometrium) has been shown to occur more frequently after the menopause in those women who have been using estrogen replacement therapy. The endometrial growth response to estrogen can be modified by the concurrent or sequential use of a progestin. This study was undertaken to determine whether the serum concentration of the endogenous sex hormones — estrone, estradiol, estriol, testosterone, androstenedione and progesterone, in women with endometrial cancer or hyperplasia who have not used estrogens is different from that in similar women without endometrial disease. Since the estrogens and testosterone circulate in two forms, unconjugated and conjugated (esterified with sulfuric and/or glucuronic acids, which alter their biologic action) these hormones were measured in both forms.

We have found that while the range of serum concentration was wide in all groups, i.e. women with and without endometrial cancer of hyperplasia (both with and without their uterus and ovaries removed), there was no difference between groups with one exception. Those women without endometrial cancer have a higher concentration of progesterone than age-matched women with the disease.

These findings suggest that: 1) in those postmenopausal women who have not used estrogen replacement therapy, adequate progesterone production may be important in prevention; and 2) that the intermittent use of a progestin may be of prophylactic value.

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*Project 367.

**Professor of Obstetrics and Gynecology, McMaster University, Hamilton.
†Associate Professor of Obstetrics and Gynecology, McMaster University.

ABSORPTION AND METABOLISM OF EQUINE ESTROGENS IN NORMAL MEN AND POSTMENOPAUSAL WOMEN*

B. R. BHAVNANI** and C. A. WOOLEVER†
Hamilton, Ontario

In the course of our investigations, the following two phases have been completed:

Radioimmunoassay of Plasma Equilin and Estrone in Postmenopausal Women After the Administration of Premarin

Conjugated equine estrogen preparations, such as Premarin, contain sulfate esters of the ring-B, unsaturated estrogens — equilin, equilenin, 17α-dihydroequilin, 17α-dihydroequilenin, 17β-dihydroequilin and 17β-dihydroequilenin classical estrogens — estrone, 17β-estradiol and 17α-estradiol. The major components are estrone sulfate (45%) and equilin sulfate (25%). They are used extensively as replacement therapy for estrogen-deficient women. Recently, they have been implicated in the genesis of some cases of carcinoma of the endometrium.

In spite of their wide use, no methods are available to measure their levels in postmenopausal women on this form of therapy. This investigation deals with the development of a simple, accurate, and specific method for the simultaneous measurement of unconjugated plasma equilin and estrone in the postmenopausal women, after either intravenous or oral administration of Premarin. Antiserum against estriol-3, 16, 17-trihemisuccinate-HSA and high specific activity [2,4-^{3}H] equilin and [6,7-^{3}H] estrone were used in the assay procedure. Specificity of the assay was achieved by separation of equilin from estrone by chromatography on micro-Celite partition columns using silver nitrate as the stationary phase. The sensitivity of the standard curves for both equilin and estrone was 10-20 pg, and the smallest amount of estrone and equilin that could be measured accurately in the plasma was 250 pg/ml for both steroids. The coefficient of variation for both steroids ranged from 1 to 8%, over a range of 250 to 5000 pg/ml plasma. The interassay coefficients of variation for equilin and estrone were 4.6% and 2.4% respectively. After the intravenous administration of 10 mg Premarin, maximum concentrations of 4 and 11.2 ng/ml for equilin and estrone, respectively, were obtained after 20 minutes. Thereafter, both steroids disappeared from the plasma gradually. When 10 mg Premarin was administered orally, equilin and estrone appeared in the blood gradually, and maximum levels of

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*Project 388.

**Associate Professor of Obstetrics and Gynecology, McMaster University, Hamilton.
†Professor of Obstetrics and Gynecology, McMaster University.

560 and 1400 pg/ml were reached after 3 and 5 hours for equilin and estrone, respectively. Equilin gradually disappeared, and by 24 hours, only small amounts (125 pg/ml) were still detectable. The levels of estrone declined more rapidly, though it was detectable after 24 hours. These preliminary results indicate that equilin sulfate is converted to circulating, unconjugated equilin in a manner similar to the conversion of circulating estrone sulfate to estrone.

This method also has the potential for the estimation of plasma equilin sulfate and estrone sulfate after chemical "solvolysis" or enzymatic hydrolysis to equilin and estrone. These studies are now in progress.

Determination of the Metabolic Clearance Rate (MCR) of Equilin Sulfate and Equilin in Normal Postmenopausal Women and Men

Conjugated equine estrogens are widely used for replacement therapy in postmenopausal women and, because equilin sulfate is one of the main components of these preparations, we have determined its MCR and metabolism in postmenopausal women and men by single injections of ^{3}H-equilin sulfate into four postmenopausal women and a normal man. Following the intravenous bolus, blood samples were drawn into heparinized tubes at various time intervals. The plasma obtained was fractionated into the unconjugated, sulfate and glucuronide fractions. The bulk of the radioactivity was present in the sulfate fraction and, from this, equilin, 17β-dihydroequilin, equilenin and 17β-dihydroequilenin were isolated, purified and their concentration measured and corrected for procedural losses. The disappearance of radioactivity as equilin sulfate can be described as a function, which is the sum of two exponentials. The mean value for the initial volume of distribution is 16 L in postmenopausal women and 18 L in men. The disappearance of equilin sulfate from this inner volume in both postmenopausal women and men has a mean T ½ of approximately 3 minutes. The mean MCR for equilin sulfate in postmenopausal women is 145±26 L/m^2/day (98-230) and that in men was 144 L/m^2/day. The mean ½ of the slower component of equilin sulfate is approximately 3 hours. Using the same experimental design, the MCR of unconjugated equilin was found to be 2340 L/m^2/day and 2470 L/m^2/day in postmenopausal women and normal men, respectively. The rate of formation of equilenin sulfate was very rapid and reached a maximum at 3 minutes, while 17β-dihydroequilin sulfate and 17β-dihydroequilenin sulfate formation reached maximum levels at 20 minutes. Essentially all of equilin sulfate and its metabolites were cleared from the circulation by 8 hours. The MCR of equilin sulfate is approximately 6% that of unconjugated equilin. The low MCR probably is due to the binding of equilin sulfate with serum albumin and perhaps other blood proteins. Whether equilin sulfate binds to these blood proteins remains to be established. The low MCR could also result if only a small fraction of the circulating equilin sulfate can be metabolized. We have shown in this study that equilin sulfate is metabolized to circulating 17β-dihydroequilin sulfate, 17β-dihydroequilenin sulfate and equilenin sulfate. Constant infusion studies are required to calculate accurately the conversion of equilin to each of its metabolites.

These studies indicate that equilin sulfate, one of the main components of Premarin, remains in the human body for a longer time than unconjugated equilin, and that it is metabolized to biologically more active estrogens such as 17β-dihydroequilenin sulfate. The physiological significance of these findings remains to be established.

CHEMOTACTIC INHIBITORS IN CANCER*

L. A. MANDELL**, *Hamilton, Ontario*

Chemotaxis refers to the directed migration of neutrophils toward a site of inflammation. Regulation of this movement depends upon both stimulatory and inhibitory mechanisms. It has been reported that chemotactic inhibitors, which are present in normal serum in minute concentrations are increased in several diseases. Our purpose is to demonstrate such inhibitors in the serum of cancer patients and to characterize their specificity and mechanisms of action. The functional definition of these inhibitors is essential to a more complete understanding of the inflammatory process and to our comprehension of the cancer patient as an immunocompromised host. Since the concentration of these inhibitors is likely to be proportional to tumor size, a parallel study is also in progress to determine whether these inhibitors may serve as markers of tumor load.

A standard method is used to measure chemotaxis with C5a and bacterial filtrate (BF) as the chemoattractants. Serum from 65 patients with various tumors at different stages of progression were tested to determine the presence of chemotactic-factor inhibitors (CFI) or cell-directed inhibitors (CDI). On a preliminary basis, lysates from tumor cells grown in cell culture have been tested as well. All results were analyzed statistically.

Patients with lung cancer and leukemia had inhibitors of chemotaxis due to CFI directed against the chemoattractant C5a but not BF. Lymphoma patients showed CFI directed against both C5a and BF. Chemotactic inhibition, due to CDI specific for C5a (as the attractant), was noted in association with lung cancer but CDI with both BF and C5a were found with leukemia and lymphoma. No CDI were detected with breast cancer. Lysates of T- and B-cell lymphomas grown in tissue culture demonstrated both CFI and CDI activity.

The results indicate that both type and specificity of chemotactic inhibitor depend upon the underlying tumor. It appears that the serum of patients with hematologic malignancies contain a broader range of inhibitor activity.

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*Project 438.

**Head, Division of Infectious Diseases, McMaster University, Hamilton.

Ontario Cancer Foundation Hamilton Clinic

CLINICAL INVESTIGATIONS

Dr. W. M. Hryniuk, Director of the Hamilton Clinic, reports on the following clinical research investigations:

ELECTRON BEAM THERAPY OF MYCOSIS FUNGOIDES

A unique combination of resources allows whole-body electron therapy of mycosis fungoides to proceed under optimum conditions at the Hamilton Clinic. Dr. A. Tadros directs the project, which attracts patients from the entire country at the rate of four new cases per month. A recent analysis of results at 10 years indicates that, while the disease is chronic — when patients die, they die of their disease. We have identified a subgroup of patients, T_2N_0, who enjoy a long disease-free survival. Identification of this subgroup, which does not require additional treatment, suggests that we may be able to employ electron-beam therapy as the sole modality. This possibility allows us to design a trial of electron therapy, plus or minus adjuvant treatment for other subgroups.

ENDORECTAL RADIATION (PAPILLON TECHNIQUE) OF RECTAL CARCINOMA

Dr. V. Basrur co-ordinates a group testing the use of endorectal radiation of selected cases of rectal carcinoma. With this technique, a small but well-defined group of patients can be spared abdominoperineal resection and colostomy.

INTENSIVE AND BRIEF CHEMOTHERAPY AFTER MASTECTOMY IN PREMENOPAUSAL STAGE II BREAST CANCER

A multiple-drug combination is being given for 12 weeks to patients under the age of 50 with axillary nodal involvement at the time of mastectomy. The study is being done in co-operation with the London Clinic and the results will be compared with historical controls treated with melphalan or radiotherapy.

COMPARISON OF TREATMENT POLICIES IN POSTMENOPAUSAL STAGE II BREAST CANCER

The role of adjuvant chemotherapy is unclear in patients over the age of 50 who have axillary-node involvement at the time of mastectomy. Accordingly, patients in this group, who are referred to the Hamilton Clinic, are randomized to see either a radiation or medical oncologist for consultation and treatment.

DRUG-SEQUENCE IN CHEMOTHERAPY OF HEAD AND NECK CANCER

Dr. G. Browman is co-ordinating a randomized trial to determine the optimum sequence for the administration of fluorouracil and methotrexate. The trial is designed to test a biochemical model describing the interaction of the two drugs.

IN VITRO STUDIES OF ACUTE MYELOBLASTIC LEUKEMIA (AML) CELLS

Dr. G. Browman is testing the in vitro sensitivity to drugs of AML cells. The same drugs are being used in an intensive chemotherapy regimen aimed at curing AML. The study is in collaboration with six American centres and the consortium is supported by NCI Grant RIO CA 28734-01.

ESCALATED BACOP/SEPTRA THERAPY OF POOR PROGNOSIS LYMPHOMAS

A combination of drugs in escalating doses is given under cover of prophylactic Septra (trimethoprim-sulfa combination) to selected patients with poor-prognosis lymphomas. A pilot study of this high-dose chemotherapy has just been completed in collaboration with the Princess Margaret Hospital in Toronto and the Manitoba Cancer Foundation in Winnipeg. A complete remission rate of 94% has been achieved in patients with marrow-positive disease. These results have prompted the development of a controlled national NCIC trial to determine the role of Septra prophylaxis in treatment of poor-prognosis lymphomas. (This study is supported by the NCIC and the following pharmaceutical manufacturers: Adria, Lederle, and Bristol.)

STUDIES IN SMALL-CELL LUNG CARCINOMA (SCLC)

Dr. A. Figueredo is co-ordinating a series of studies to define the optimum treatment of SCLC. The present study is a randomized trial of regular-dose versus high-dose chemotherapy under cover of Septra. The results indicate that the use of prophylactic Septra allows higher doses of drugs to be administered. Whether this can be translated into improved remission rates and longer survival remains to be determined.

STUDIES IN OVARIAN CANCER

A new pilot study of weekly intensive Adriamycin/cis-platinum therapy of Stages III and IV ovarian cancer has just been closed. Preliminary analysis suggests that the results are much superior to the usual regimen of cyclophosphamide/Adriamycin/cis-platinum given every four weeks.

CO-OPERATIVE GROUP TRIALS

Selected protocols of the NCIC and NSABP are being followed for myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, non-small-cell carcinoma of the lung, melanoma, ovarian carcinoma and breast cancer.

Ontario Cancer Foundation Kingston Clinic

CLINICAL INVESTIGATIONS

Dr. J. S. Lott, Director of the Kingston Clinic, reports on the following clinical research investigations:

COMPENSATOR DESIGN

Dr. P.C. Shragge and associates have developed new computer programs, which can calculate dose distributions, taking into account both irregular field shapes and individual patient contours. These same programs can be used to design sophisticated beam-flattening filters. These investigators are proceeding with experimental verification of these programs in a clinical setting.

CARCINOMA OF THE PROSTATE

Under the direction of Dr. Peter Froud, a group is continuing to study the effectiveness of Iodine 125 seed implant for primary prostatic carcinoma and are comparing it with 20 MeV photon irradiation in patients who have had a staging laparotomy and lymphadenectomy.

CARCINOMA OF THE CERVIX

Using a historical control group, Dr. J.A. Carmichael of Queen's University, in collaboration with the Kingston Clinic staff, is comparing the Wertheim hysterectomy and conventional radiotherapy in Stages Ib and IIa carcinoma of the cervix.

CARCINOMA OF THE BREAST

Under the direction of Dr. E.E. Sterns, a group is testing aminoglutethemide as alternative to adrenalectomy in patients with advanced carcinoma of the breast.

CARCINOMA OF THE RECTUM

Using historical controls, members of staff are assessing the value of short-term preoperative radiation in patients with carcinoma of the rectum.

APPLICATION OF CT SCANNING

Dr. Lott and staff are studying the application of CT scanning in radiation treatment planning using the Kingston General Hospital whole-body scanner.

NATIONAL TRIALS

The Kingston Clinic staff are co-operating in the following National Cancer Institute of Canada studies:

Carcinoma of the ovary
Hodgkin's disease
Non-Hodgkin's lymphoma

Queen's University, Kingston

REGULATION OF GRANULOPOIESIS IN LEUKEMIA*

P. R. GALBRAITH**, *Kingston, Ontario*

The objective of this study is to understand negative-feedback, control mechanisms which regulate granulopoiesis, and utlimately to determine how these mechanisms may be exploited by the progeny of a single mutant cell which gives rise to clonal hemopathies such as leukemia. It is now well known that specific neutrophilic granules contain lactoferrin, an iron-containing macromolecule, with diverse in vitro effects, one of which appears to be to suppress the production of colony-stimulating activity (CSA) — a family of glycoproteins thought to provide stimulation of granulopoiesis. Lactoferrin is released slowly from degranulating neutrophils and has been purported to be the most important feedback regulator.

However, we have found two additional inhibitory activities both of which are rapidly and spontaneously released from normal neutrophils, and are separated by a simple membrane (cut-off point at 12,000 daltons of molecular weight). The higher-molecular-weight material blocks the response of colony-forming cells (CFC) and their progeny to CSA but does not interfere with its production. The low-molecular-weight activity inhibits recruitment of CFC subsets with the highest self-renewal capacity but has no effect on other cells. It apparently arrests these cells in G_1 (or G_0) of the cell cycle. These conclusions are based on the results of kinetic studies during which sequential changes in the size distributions of all granulocytic aggregates were recorded. Studies are in progress to determine if these inhibitory activities are mediated by a direct action of proliferating cells or are mediated by accessory cells. For this purpose we have developed assays using monoclonal antibodies (and complement) to delete specific subpopulations of mononuclear leukocytes. Preliminary evidence suggests the higher-molecular-weight inhibitory activities act directly. Efforts to identify this material are planned. We have been unable to isolate the low-molecular-weight inhibitory activity probably because it is so labile.

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*Project 309.

**Professor of Medicine, Division of Hematology, Queen's University, Kingston.

IMMUNOCHEMICAL AND BIOCHEMICAL MARKERS IN PROSTATIC DISEASE*

A.W. BRUCE** and D.E. MAHAN†
Kingston, Ontario

Over the last few years, tumor markers have been under intensive investigation in the hope of improving the diagnosis and management of adenocarcinoma of the prostate. Prostatic fluid is an enriched source of secretory prostatic antigens. Malignant alterations in the gland may be detected by changes in the levels of eutopic protein markers or by the appearance of ectopic antigens in prostatic fluid. It has been reported that the protein composition of prostatic fluid shows alterations in patients with this neoplasm[1].

Recently we have evaluated several potential markers in the prostatic fluid of patients with prostatic disease. Total acid phosphatase, c3, transferrin, lactoferrin, and total protein were measured in patients with adenocarcinoma of the prostate (13), prostatitis (22), benign prostatic hyperplasia (48), prostatism (63), miscellaneous non-malignant diagnoses (41), and controls (18). Levels of total prostatic-fluid protein were elevated in patients with adenocarcinoma. Specifically, concentrations of the proteins c3, transferrin, and lactoferrin were increased in the prostatic fluid of these patients. A correlation was noted between the levels of acid phosphatase, transferrin and protein concentration in several groups of patients. Others have reported elevated levels of immunoglobulin in the prostatic fluid of prostatic cancer patients[1]. This suggests generalized deregulation of protein synthesis and/or secretion by the epithelial cells lining the prostatic acini as opposed to increased synthesis of specific protein(s). This greatly impairs the usefulness of eutopic proteins as markers of neoplastic disease.

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*Project 390. (Final Report)

**Professor and Chairman, Department of Urology, Queen's University, Kingston.
†Lecturer in Urology and Biochemistry, Queen's University.

FUNCTION AND AUGMENTATION OF CYTOTOXICITY IN GENITOURINARY CANCER*

A. MORALES**, *Kingston, Ontario*

We have continued our studies on immunotherapy for tumors of the genitourinary tract. The results we reported initially are now supported by the results of randomized, controlled trials in which our initial protocols have been strictly duplicated[1,2].

This project has been designed to study changes in immune reactivity induced by immunomodulators. Initially it was determined that immunotherapy induces profound alterations in natural cytotoxicity. It has been our belief, however, that current methods of assessing natural cytotoxicity are cumbersome and impractical in the clinical situation. We have developed a whole-blood assay, which differs fundamentally from standard assays and is both sensitive and suitable for monitoring immune reactivity[3]. The assay has been found valuable in the clinical setting. We are now in the process of developing a standard of frozen effector cells in order to normalize the daily variations, which at present keep us from using cytotoxic assays for the linear monitoring of cancer patients. We are well advanced in this endeavour and, within the next year, expect to improve further the quality and usefulness of this novel assay.

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*Project 391.

**Professor and Chairman, Department of Urology, Queen's University, Kingston.

NATURAL KILLER (NK) CELL FUNCTION IN HUMAN MALIGNANT DISEASE: BASIC AND CLINICAL STUDIES*

H.F. PROSS**, *Kingston, Ontario*

Natural killer (NK) cells are lymphocytes, present in virtually all normal individuals, which are capable of rapidly lysing tumor cells in vivo and in vitro in the apparent absence of disease, prior sensitization, or deliberate immunization of the lymphocyte donor[1]. In the past year there has been a phenomenal increase in our knowledge of the characteristics and function of these cells, and it is now believed that they may represent a fundamental host mechanism relevant to hematopoiesis, surveillance against neoplasia, "immune" defense against metastatic cancer, and early reactivity against viral infection. The cells are not "classical" B or T cells and their function is intact in persons with many immunodeficiencies involving these cells.[2] In contrast, the NK activity of patients with advanced malignancy is suppressed.[3]

In the past year, we have completed our analysis of normal variables affecting cytotoxic function. As noted in a preliminary report in this publication last year, 539 normal healthy donors were tested from once to 213 times over a seven-year time span[4]. NK activity did not vary with blood group, Rh type or HLA type. There was a slight increase in NK activity from birth to adulthood with no decrease in the elderly. The relative NK activity of individual donors was consistent over the years — an important observation in terms of our concurrent analysis of cancer patients. It was also found that the data fitted certain mathematic models of cytotoxicity[4,5] and that, in general, when NK-cell activity of a particular donor was high other tumor cells also were sensitive. The differences between high and low normal donors could be attributed to differences in the frequency of blood killer cells, as opposed to differences in efficiency of the cells[6]. It was also found that normal lymphocytes, which bind to tumor cells[7], are a heterogeneous population including lytic and non-lytic T and non-B, non-T lymphocytes[8]. In cancer patients it is possible to detect abnormalities in NK function as well as frequency[8], and currently we are evaluating studies on the relationship of NK dysfunction, if any, to survival, disease-free interval and metastatic disease, etc.

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*Project 392.

**Ontario Cancer Foundation Research Associate, Ontario Cancer Foundation Kingston Clinic; and Associate Professor of Radiation Oncology, and of Microbiology and Immunology, Queen's University, Kingston.

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CLINICAL TRIAL OF HEMATOPORPHYRIN PHOTORADIATION THERAPY FOR CANCER*

J.C. KENNEDY**, *Kingston, Ontario*

Since the present clinical trial of hematoporphyrin-derivative, photoradiation therapy began in 1978, we have treated 41 patients. Some were treated in collaboration with Dr. C. Tanser of the Hamilton Clinic. The 37 primary, basal-cell carcinomas were distributed among 3 patients. The remaining 38 patients had multiple secondaries of the 8 other histological types, indicated below. The number of secondaries treated per person varied from one to several hundred, and their size ranged from barely palpable nodules to massive tumors several centimeters thick. The intracutaneous and subcutaneous secondaries were located anywhere from the crown of the head to the soles of the feet. Other tumors were located within cavities formed by the operative removal of the eye or nasal sinuses, or in the vaginal vault.

We have developed a new type of light delivery system for tumors located deep within the vagina and found it to be effective both for its intended purpose and for tumors located elsewhere. Also, a new type of light source and light delivery system is being developed for use against early multicentric carcinoma of the bladder.

Histologic Type of Cancer	Number of Patients Treated	Response
Basal-cell carcinoma	3 (37 primaries)	22 excellent; 15 good
Squamous-cell carcinoma of the skin	3	3 poor
Squamous-cell carcinoma of the mucous membranes	5	1 good; 4 poor
Malignant melanoma	5	1 excellent; 1 good; 3 poor
Kaposi's sarcoma	2	1 excellent; 1 fair
Breast carcinoma	19	4 good; 11 fair; 4 poor
Endometrial carcinoma	1	good
Ovarian carcinoma	1	fair
Retinoblastoma	1	good
Lung carcinoma	1	fair

excellent: complete regression with a single treatment

good: complete regression, but required more than one treatment; or complete regression, but eventually recurred

fair: regression substantial but not complete

poor: little, if any, benefit to the patient

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*Project 441. (Continuation of Projects 352 and 369)

**Ontario Cancer Foundation Research Associate, Ontario Cancer Foundation Kingston Clinic; and Associate Professor of Radiation Oncology and Pathology, Queen's University, Kingston.

Ontario Cancer Foundation London Clinic

INVESTIGATION OF PHYSICAL RADIATION PARAMETERS*

D.J. DAWSON**, *London, Ontario*

During the past year, extensive measurements have been undertaken in the beam penumbral regions for ^{60}Co, 6MV and 31MV x-rays from an AECL Theratron 780, and AECL Therac 6 and a Brown Voberi betatron. The measurements have been carried out by J.M. Harper, a graduate student in the Department of Physics at the University of Western Ontario, in partial fulfillment of the requirements for the degree of Master of Science.

The measurement system has involved the use of a solid state diode and two ionization chambers as the dosimetric system, in combination with a stepping motor-drive system capable of 0.1 mm steps.

A comparison of these dosemeters has shown that the ionization chambers, frequently employed for clinical comparisons, are not capable of sufficient resolution in the penumbral region of ^{60}Co and 6MV x-ray beams.

A theoretical approach, using an in-house PDP1103 computer, has been undertaken to gain a clearer understanding of this phenomenon. The computer simulation studies have determined effective diameters for these dosemeters as a function of beam energy. These effective diameters can determine the penumbral degradation associated with these dosemeters.

Measurements in air have indicated a linear increase in penumbral width with distance from the source. When these penumbral widths are extrapolated back to the collimator position, a finite width is determined. This represents the first measured deviation from the geometric law and has been termed an inherent penumbra. The inherent width has been associated with the finite dimensions of the dosemeter and the source-collimator configuration.

The effect of scatter from a surrounding medium has been studied in a water phantom. These measurements more nearly reproduce the dose distributions, which pertain in patients undergoing radiotherapy. The broadening of the penumbra at depth has been delineated as a function of beam quality.

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*Project 266.

**Senior Physicist, Ontario Cancer Foundation London Clinic; and Associate Professor of Therapeutic Radiology, and Sessional Lecturer of Physics, University of Western Ontario, London.

COMBINED MODALITY TREATMENT OF CANCER USING MULTICELL SPHEROIDS AND TRANSPLANTED TUMORS IN MICE*

W.R. INCH**, *London, Ontario*

Chinese hamster V79 fibroblasts normally grow as a monolayer culture on petri dishes; they can also be grown as multicell spheroids when the cells are placed in spinner culture flasks. The spheroid is a convenient in vitro model of a tumor and can be used to test the cytotoxicity of treatment modalities such as ionizing radiation, drugs and hyperthermia.

The microenvironment of a large spheroid is similar to that of a solid tumor, which has outgrown its blood supply. Cells in the outer zone are well nourished and dividing rapidly, those in the inner layers are poorly nourished, lack oxygen and only a few are dividing, while the central area will be necrotic. The non-dividing, poorly nourished cells are resistant to treatment and probably lead to the local recurrence of the tumor.

Butylated hydroxyanisole [2,(3)-tertbutyl-4-hydroxyanisole (BHA)] is an antioxidant, which is only slightly soluble in aqueous solution but, following large doses, it is absorbed readily from the gastrointestinal tract and concentrates in body fat. We have studied the effect of this drug on the viability of exponentially growing V79 cells and on the radiation survival of multicell spheroids. BHA at concentrations of 0.1 mM had little effect on cell viability for exposure times of up to five hours; at 0.5 mM there was a 10% decrease in viability after three hours.

The presence of 0.1 mM for one hour before and during irradiation did not increase the radiosensitivity of cells in 800μ diameter V79 multicell spheroids. Spheroids treated with 0.5 mM had a significantly decreased survival. This concentration appeared to be dose modifying, that is, there was a decrease in the shoulder region of the survival curve as well as an increase in the final slope.

It was concluded that BHA may be useful as a radiosensitizing chemical for the treatment of solid tumors by radiotherapy.

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*Project 393.

**Experimental Oncologist, Ontario Cancer Foundation London Clinic; and Professor of Radiation Oncology and Biophysics, University of Western Ontario, London.

ADDITIONAL INVESTIGATIONS

In addition to the research projects being conducted at the Ontario Cancer Foundation London Clinic, for which grants have been approved, Dr. Haydn Bush, Director of the London Clinic, reports on the following clinical research investigations:

NATIONAL TRIALS

In co-operation with the National Cancer Institute of Canada, the staff of the London Clinic is participating in the following studies:

- Alternative methods of treatment of myeloma.
- Melanoma adjuvant immunotherapy study, plus a study of combination chemotherapy in advanced myeloma.
- Carcinoma of the ovary — participation in OV2 and OV4.
- Advanced carcinoma of the breast.

CLINICAL TRIALS UNIT

A number of retrospective studies have been performed to assist in the planning of future prospective clinical studies and trials.

ADJUVANT STUDY IN CARCINOMA OF THE BREAST

In co-operation with the Hamilton Clinic, combination chemotherapy is being conducted in postmastectomy patients with auxilliary metastases. We expect that this study will be expanded to include postmenopausal women, although at the present time, only premenopausal women (under the age of 50) are eligible for the study.

University of Western Ontario, London

A COHORT STUDY OF THE EFFECT OF AGE AT FIRST FULL-TERM BIRTH UPON THE RISK OF DEATH FROM BREAST CANCER*

K.M. STAVRAKY**, *London, Ontario*, M.E. SMITH†, *Ottawa, Ontario*
A.E. DONNER‡, *London, Ontario*
J.R. MILLER‡‡ and S.H. UH††, *Vancouver, B.C.*

The increasing risk of breast cancer with increasing age at which a woman bears her first full-term child was clearly shown in an international collaborative study carried out in seven different centres[1,2]. This study estimated that women who bear their first child under the age of 18 have about one-third the risk of breast cancer than those whose first child was born at the age of 35 or later. The investigations that formed the international study were all case-control interview studies, which attempted to identify all cases of breast cancer in the defined areas; controls were patients hospitalized for diseases other than breast cancer in the same hospital as the cases.

However, more recent case-control studies have shown that the relationship is not consistent[3-5] and, for this reason, a large cohort study has been carried out. In this study, women who bore their first child in British Columbia between the years 1950 and 1973 were identified, and grouped according to their ages at the time of first birth. Record-linkage techniques identified all deaths among these women, which occurred in British Columbia. Among 273,284 women, whose records of first birth were entered into the study, 2584 deaths from all causes have been identified, of which 215 were due to breast cancer.

Analysis so far suggests that the expected relationship between age at first birth and risk of death from breast cancer is present among women 50 years old or more. No such relationship is evident for other causes of death. We are now awaiting additional data from British Columbia to complete the analysis of the breast cancer death and other deaths at ages below 50. The linkage of the British Columbia birth records to the National Death Index, which will locate as many women as possible who died in other parts of Canada, is not complete.

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*Project 333.

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‡Associate Professor of Epidemiology and Biostatistics, UWO.

‡‡Professor of Medical Genetics, University of British Columbia, Vancouver, B.C.

††Department of Medical Genetics, UBC.

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THE EFFECT OF SOCIOECONOMIC STATUS ON THE PROGNOSIS OF CANCER OF VARIOUS SITES*

K.M. STAVRAKY**, *London, Ontario and*
J.E. KINCADE†, *Chapel Hill, NC, USA*

The purpose of this study is to determine whether socioeconomic status (SES) has an effect on the prognosis of cancer of several sites, especially breast, lung, large bowel, endometrium, cervix, skin (melanoma), and the lymphatic system (lymphomas). In particular, we are testing the hypothesis that cancer has poorer prognosis (high recurrency rates or low survival rates) among persons of low SES than among persons of high SES, even when other important factors such as stage of disease and method of treatment are the same.

Interviewing in the Ontario Cancer Foundation Clinics in London and Hamilton is now complete. Slightly more than 2000 patients in both clinics co-operated. The interview obtains information on SES (education and occupation), the presence of other chronic debilitating disease, stressful life events, availability of social support, and general personality characteristics, which might influence a person's ability to cope with serious illness.

Collection of necessary information from clinic charts on pathologic diagnosis, stage of disease at diagnosis and initial treatment is continuing. We have begun collecting information on the status of each patient one year after the beginning of treatment. No data analysis will be available for at least one year.

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*Project 420.

**Ontario Cancer Foundation Research Associate; and Associate Professor of Epidemiology and Biostatistics, University of Western Ontario, London.

†Assistant Professor of Nursing, University of North Carolina, Chapel Hill, N.C.

Ontario Cancer Foundation Ottawa Clinic

CLINICAL INVESTIGATIONS

Dr. G.E. Catton, Acting Director of the Ottawa Clinic, reports on the following clinical research investigations:

BREAST CANCER

- Drs. R.S.R. McDermot and J.E. Devitt are contributing to the NSABP protocols for the evaluation of segmental mastectomy (with and without radiotherapy) versus total mastectomy in Stage I breast cancer, and to the addition of adjuvant chemotherapy to these modalities in Stage II breast cancer.
- Drs. W.E. Hirte, L.L. Stolbach, C. Cripps and V. Young are contributing patients to NSABP protocols to determine the effect of adjuvant chemotherapy and hormonal therapy in breast cancer patients according to age of patient, stage of disease, and estrogen and progesterone receptor status. These studies include both node-positive and node-negative patients.

NATIONAL TRIALS

The Ottawa Clinic participates in the following studies of the National Cancer Institute of Canada and the Cancer Research Co-ordinating Committee:

- Adjuvant immunotherapy in early melanoma.
- Treatment of Stages I and IIa high risk, or Stages IIb or IIIo carcinoma of the ovary after total hysterectomy and bilateral salpingo-oophorectomy.
- Adjuvant immunotherapy in Duke's B_2 and C colorectal cancer.
- Adjuvant immunotherapy in resected bronchogenic carcinoma.
- Treatment of plasma-cell myeloma with chemotherapy.

EASTERN CO-OPERATIVE ONCOLOGY GROUP

The Ottawa Clinic has continued to contribute to the Eastern Co-operative Oncology Group in the following areas: Participation in group meetings; membership in Site and Modality Steering Committees; and in patient accrual.

LOCAL CLINICAL TRIALS

- Cisplatin plus cytosine arabinoside with and without caffeine for glioblastomas, and head and neck carcinoma.
- Metronidazole plus chemotherapy for a variety of tumors.

- Biochemically-sequenced methotrexate and 5-fluorouracil for a variety of neoplasms.
- Intracarotid infusion of BCNU, cisplatin, VM-26 for intracerebral tumors.
- Intrathecal methotrexate, cytosine arabinoside, hydrocortisone plus thio-TEPA for meningeal involvement by malignancies.
- Intra-arterial cisplatin with and without disulfiram for localized bladder carcinoma.
- Treatment of advanced head and neck cancer with methotrexate, bleomycin and cisplatinum.
- Treatment of advanced prostate with Adriamycin, cyclophosphamide plus flutamide.

PHARMACOLOGY STUDIES

The following studies are being conducted in the Cancer Research Laboratory at the Ottawa General Hospital:

- Human, autopsy-tissue distribution of chemotherapy agents and their metabolites – VP-16, VM-26, mitomycin-C, cisplatin, cytosine arabinoside, etc.
- Penetration of antineoplastic agents – VP-16, VM-26, cisplatin, cytosine arabinoside, etc., into intracerebral tumors.
- Plasma pharmacokinetics of VP-16, VM-26, mitomycin-C.
- Bioavailability of oral VP-16.
- Relationship of plasma and tissue pharmacology of cisplatin to cisplatin-induced nephrotoxicity.

University of Ottawa

STUDIES ON POLYAMINE AND CYCLIC NUCLEOTIDE METABOLISM IN CANCEROUS PROSTATE*

R. L. SINGHAL**, *Ottawa, Ontario*

In recent years, there has been considerable interest in examining the role of polyamines in the control of growth processes, both in normal and in tumor tissues. Also a relationship has been demonstrated between polyamines, testicular hormones and growth of the prostate glands[1,2]. Furthermore, we demonstrated earlier that cyclic adenosine monophosphate (AMP) is involved in the action of androgens on the secondary sex organs[3]. Our studies[4] led to the isolation and characterization of cyclic AMP-dependent protein kinase from normal and prostate tumor.

To understand more clearly the role of polyamines and cyclic AMP-adenylate cyclase system in the growth of prostate tumor, we extended our studies to the determination of the level of the three polyamines, i.e. putrescine, spermidine and spermine, and the activity of the two synthesizing enzymes, i.e. ornithine decarboxylase and adenosyl methionine decarboxylase after a variety of hormonal manipulations both in normal and cancerous tissues. The amount of cyclic AMP and the levels of adenylate cyclase were also measured during the growth of the tumor.

Methylcholanthrene-induced squamous epithelial cell carcinoma was implanted under the skin of both normal and castrated animals. We examined the effects of estrogen, androgen and the antiandrogen – cyproterone acetate, on the levels of polyamines, cyclic AMP and their synthesizing enzymes.

Castration at 7 days produced a marked decrease in the amounts of the three polyamines and the activity of the two synthesizing enzymes. In animals castrated 7 days earlier, androgen replacement for 3 to 7 days raised the prostatic content of polyamines and the activity of the enzymes to almost normal limits. Administration of cyproterone acetate to non-castrated animals for 7 days produced effects similar to those observed after castration. Estogen treatment of castrates did not modify polyamine metabolism in comparison to normals. Castration, androgen replacement and treatment with cyproterone acetate or estrogen had effects on cyclic AMP-

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*Project 421.

**Professor and Chairman, Department of Pharmacology, School of Medicine, University of Ottawa.

adenylate cyclase system similar to those seen in the case of polyamines and their synthesizing enzymes.

In tumor tissues obtained from non-castrated and castrated animals 11 days after implantation, the levels of the three polyamines and the activity of their synthesizing enzymes were almost similar. Administration of estrogen or cyproterone acetate did not produce any significant change in polyamine levels. Tumor tissue obtained 21 and 30 days after implantation showed a gradual decline in the levels of polyamines, which might be due to some necrosis of the tumor tissue. The level of cyclic AMP and adenylate cyclase activity was higher in tumor tissue then in the normal prostate. In this case also, treatment with testosterone, estrogen or cyproterone acetate did not significantly alter the content of cyclic nucleotide. Furthermore, tumors implanted in castrated animals showed a growth rate similar to normal subjects.

Our recent work demonstrates that methylcholanthrene-induced squamous epithelial cell carinoma has little or no androgen dependency. Androgen treatment does not exert much effect on polyamine and cyclic AMP levels in this rapidly growing tumor of the prostate. The data accumulated thus far suggest that the hormonal regulating mechanisms underlying polyamines and cyclic AMP metabolism in the prostatic tumor differ from those operating in the normal prostate.

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Ontario Cancer Foundation Thunder Bay Clinic

STUDY OF POSTRADIATION CHANGES IN LUNG USING COMPUTERIZED TOMOGRAPHY*

J. F. KOTALIK**, *Thunder Bay, Ontario*

The aim of radiotherapy of cancer is to cause maximal damage to tumor and minimal damage to surrounding normal tissue. While tumor size often can be measured after radiation, usually there is much less quantitative information about the effect of normal tissue because adequate assays are not available.

Lungs are often irradiated in the process of treating bronchogenic carcinoma, cancer of breast, and other malignancies. Known sequellae of highdose radiation, e.g. pneumonitis and lung fibrosis, can be studied as a function of time, dose, and volume treated using roentgenography but usually no quantitative in vivo assessment is possible. If the radiation oncologist could measure lung changes, he could determine the optimal total dose, size of fraction, interval between fractions, and total time, and thus achieve maximal sparing of lung tissue without reducing the destructive effect on the tumor.

We have started to investigate the feasibility of such an assay using a computerized tomographic scanner. Selected patients scheduled for radiotherapy to the thorax for cure or palliation will have a CT scan before radiotherapy, a month after radiotherapy, and then monthly for up to one year. A region of interest in the lung will be selected and unirradiated portions of the lung will serve as a control. The total lung volume will also be calculated. These postradiation changes will be examined as a function of time in relationship to the dose of radiation as calculated by the treatment planning computer.

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*Project 462.

**Director, Ontario Cancer Foundation Thunder Bay Clinic.

Hospital for Sick Children, Toronto

HETEROGENEITY OF ACUTE LYMPHOBLASTIC LEUKEMIA OF CHILDHOOD*

E. W. GELFAND**, H-D. M. DOSCH† and M. LETARTE‡, *Toronto, Ontario*

We have continued to study the heterogeneity of acute lymphoblastic leukemi (ALL) of childhood using a combination of immunologic and biochemical markers. The goal of the study is to understand the heterogeneity of the disease and to derive new insights, which may help to answer questions concerning prognosis and treatment.

In the last two years, we have studied more than 50 patients with common ALL (non-T, non-B ALL). To understand the heterogeneity of the condition, we have carried out parallel quantitations of the number of Ia and common ALL antigenic sites using a cellular radioimmunoassay. These studies have shown significant variability in the expression of these two cell markers, and we are following the clinical courses of these patients to determine whether high or low values are related to prognosis.

In addition, the cells of these patients have been incubated with tetradecanoylphorbol acetate to determine their susceptibility to this agent as measured by alteration in numbers of antigenic sites, stimulatory capacity in mixed lymphocyte reactions, and changes in cell volume. These studies further confirm the heterogeneity of this group and may provide a means for classification, prognosis, and design of specific treatment regimens.

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*Project 397.

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SIMULTANEOUS QUANTITATION OF METHOTREXATE AND 7-HYDROXYMETHOTREXATE BY HPLC*

S. J. SOLDIN** and S. M. MacLEOD†, *Toronto, Ontario*

The development of an HPLC assay with UV spectrophotometric detection (305 nm) for the simultaneous quantitation of MTX and 7-OH-MTX in serum is completed. The serum sample (300 μl) and internal standard, 8-cholorotheophylline (8-CT) are applied to SEP-PAC C-18 cartridges (Waters Associates, Inc., Milford, Mass.) in 5 ml of 0.2 M acetate buffer, pH 5.0. After a wash of 10 ml H_2O, the compounds are eluted from the cartridges in 1 ml methanol. The methanol is evaporated and the residue is reconstituted in 5 mM HCl before injection. The conditions of analysis are summarized in Table I. Recovery, precision, sensitivity and specificity data are presented in Tables II, III, IV and V respectively. Using 300 μl of serum the maximum sensitivity is 0.06 μM for MTX and 0.12 μM for 7-OH-MTX. A typical chromatogram of a patient's serum sample, 24 hours after MTX administration, is shown in Figure 1.

A comparison of our HPLC procedure with EMIT (Syva Co.) and a radiochemical-ligand binding (CP13) assay for TMX[1] produced the following results:

y	x	[MTX]	n	Slope	Intercept	r
HPLC	CPB	0-500 μM	72	0.85	3.19	0.965
HPLC	EMIT	<100 μM	29	0.96	0.17	0.984
HPLC	EMIT	>100 μM	25	0.60	45.52	0.882

These results demonstrate that the CPB and EMIT assays are not completely specific for MTX.

The serum assay has been adapted for urine samples by introducing a pre-SEP-PACK clean-up step. The assay is being evaluated for recovery and precision.

The second phase, pharmacokinetics, has been initiated on serum samples. A concentration-time profile is presented in Figure 2. As well as determining each patient's pharmacokinetics, 24- and 48-hour serum samples are analyzed on each subsequent MTX administration. Six consecutive 12-hour urine collections are obtained for future analysis.

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*Project 422.

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†Head, Clinical Pharmacology Division, HSC.

TABLE I

Optimal Conditions for Analysis

Mobile phase:	85/15 mixture of Reagent A/acetonitrile where Reagent A is 10 mM phosphate buffer pH 4.5
Column temperature:	room temperature
Column pressure:	<2000 psi
Flow rate:	0.8 ml/min
Absorbance wavelength:	305 nm
Absorbance, full scale:	0.02
Chromatography time:	<10 min

Fig. 1. HPLC chromatogram of patient sample obtained 24 hours after beginning of MTX infusion: 1.12 µM MTX, 15.94 µM 7-OH-MTX.

TABLE II

Recovery Studies (n = 15)

Concentration (μM)			Recovery (per cent)		
MTX	7-OH-MTX	8-CT	MTX	7-OH-MTX	8-CT
2.31	4.35	97.08	78.3	67.6	83.6
0.91	1.23	97.08	81.2	76.1	79.6
0.23	0.48	97.08	84.9	72.8	84.3
			X 81.5	72.2	82.5
			SD 3.3	4.3	2.5

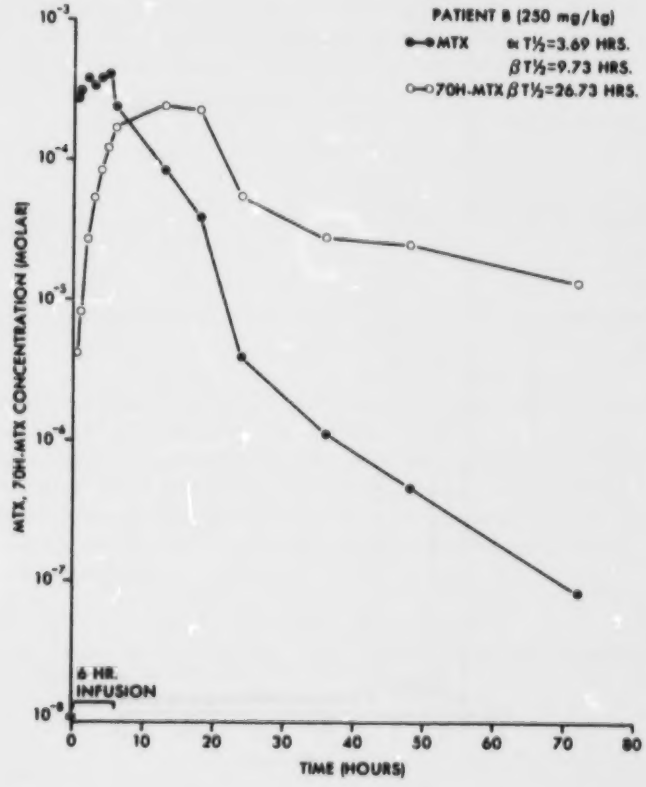

Fig. 2. MTX and 7-OH-MTX serum profiles of Patient B during and after a 6-hour infusion of 250 mg/kg MTX.

TABLE III

Precision Study (n = 20 days)

Concentration (μM)		Coefficient of Variation
MTX	2.76	8.6%
	0.97	8.2%
	0.25	15.1%
7-OH-MTX	4.40	8.9%
	1.55	7.9%
	0.53	7.6%

TABLE IV

Sensitivity (300 μl serum)

MTX	7-OH-MTX
0.06 μM	0.12 μM

TABLE V

Specificity

No interference:	folic acid
	leucovorin
	MTX mono-γ-glutamate
	MTX di-γ-glutamate
	fluorouracil
	vincristine
	doxorubicin
	cyclophosphamide
	chlorpromazine
	nabilone
	diphenylhydantoin
	phenobarbital
	primidone
	carbamazepine
	ethosuximide
	theophylline
Possible interference:	dimenhydrinate (Gravol)
	retention time is between 7-OH-MTX and 8-CT

Ontario Cancer Institute incorporating the Princess Margaret Hospital, Toronto

TOXICITY STUDY OF METRONIDAZOLE: HYPOXIC-CELL RADIATION SENSITIZER*

G. M. THOMAS** and R. S. BUSH†, *Toronto, Ontario*

The presence of relatively radioresistant hypoxic cells in human tumors may be one cause of failure to control some tumors with radiation.

It is not possible to increase the doses of radiation employed because of the limiting tolerance of the surrounding normal tissues. Therefore we have undertaken studies of compounds, which can act to sensitize hypoxic cells to the effects of radiation. The compound studied in this trial was misonidazole. Before evaluating the efficacy of this drug in combination with radiation therapy, it was necessary to obtain detailed acute toxicity data on its use with radiation and to establish a tolerable dose of drug.

Sixty-four patients with carcinoma of the cervix were randomized, double blind, to receive either placebo or misonidazole capsules daily with pelvic irradiation. Groups of patients were studied sequentially at escalating doses of misonidazole from 0.15 g/M^2 to 0.45 g/M^2 daily (total of 9.9 g/M^2). Detailed toxicity data were obtained and correlated with pharmacokinetic parameters, which were measured on each patient.

It was determined that the maximal daily dose of misonidazole, which could be administered as outlined, was 0.45 g/M^2 (total 9.9 g/M^2). At this dose, 50% of patients developed a reversible sensory peripheral neuropathy, which was of clinical significance in 35% of patients. These data have been used to design a Phase III trial to determine whether the addition of misonidazole to pelvic irradiation for patients with carcinoma of the cervix will improve pelvic disease control and cure rates over those receiving pelvic irradiation alone.

A similar toxicity study of misonidazole and radiation is going on in patients with carcinoma of the head and neck. The maximal tolerable dose of drug has not yet been ascertained.

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*Project 376.

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PROSPECTIVE STUDY OF POSTOPERATIVE THERAPY IN EPITHELIAL OVARIAN CANCER*

A. J. DEMBO** and J. F. G. STURGEON†, *Toronto, Ontario*

This project was conducted at the Princess Margaret Hospital, Toronto, and has three major components.

Radiation Therapy. One hundred and fifty-six patients with Stages IB, II and III who had a small or no postoperative tumor residuum received 2250 rads of pelvic irradiation. After stratification and random assignment, they were treated by one of two techniques of abdominopelvic irradiation, that is, 2250 rad, moving strip or open beam. Early analysis of results shows that survival and relapse-free rates are similar ($p>0.45$) but serious late treatment complications were more common in the group treated by moving-strip irradiation, indicating an improved therapeutic ratio for the open-beam technique.

Chemotherapy. One hundred and twenty patients with Stage IV and Stage III with large residual tumor masses were stratified and randomly allocated to receive melphalan, or hexa-CAF (hexamethylmelamine, cyclophosphamide, methotrexate, fluorouracil), or CAP (cyclophosphamide, Adriamycin, cisplatin). Responses occurred more frequently and were of longer duration in the patients treated with combination chemotherapy (especially CAP), but did not result in improved cure-rates. Complete responses as defined at negative "second-look" operations, and survival times were similar for all three regimens. CAP used as second-line therapy after relapse on the other regimens extended survival time after relapse[1].

Prognostic Factors. Since April 1971, clinical, pathological and treatment information has been collected on all postoperative, previously untreated patients referred for therapy. Multivariate analysis has helped elucidate the complex inter-relationships of pathology subtype and tumor grade[2], and between histology and other prognostic factors such as stage, residuum and age[3]. This information has been used to optimize treatment selection and will be incorporated in the design of the next generation of treatment studies.

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*Project 398.

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LEUKEMIA PROGRAM AT THE ONTARIO CANCER INSTITUTE*

E. A. McCULLOCH** and J. E. CURTIS†, *Toronto, Ontario*

The close association between clinical and laboratory studies of leukemia continues. The third sequential clinical trial of AML treatment (Adriamycin, Ara-C and thioguanine) nears completion. A preliminary examination of the data discloses patterns of successful remission induction and survival, which are not statistically different from those seen in earlier trials using less aggressive treatment. This clinical observation supports the view that the biological characteristics of the malignant clone in each patient are important determinants of clinical outcome. One such characteristic — the capacity of blast progenitors to undergo self renewal, has been shown, in earlier studies, to contribute to the patient-to-patient variation in clinical outcome[1]. This correlation continues in the recent series, providing evidence that, as a predictor of poor outcome, the increased self-renewal capacity is independent of the chemotherapeutic regimen employed.

The self renewal of blast progenitors was discovered in the process of investigating colony formation in culture by blast progenitors[2]. Now attention is turned to a second process, which occurs during colony formation, namely, the terminal divisions that end in proliferatively inert blast cells. Studies using monoclonal and well-characterized heterosera have shown that these divisions are associated with changes in differentiation marker frequency; this observation supports the view that blast cells follow differentiation programs; these differentiation programs resemble those of normal cells in that they yield cells incapable of division. We have proposed[3] that they differ from normal programs in that components occur in abnormal assemblages.

Recently, support for this view has been obtained from studies, which demonstrated that individual blast cells may exhibit, simultaneously, markers of more than one differentiation lineage. In normal controls examination of cell phenotypes supports the concept of lineage fidelity; that is, if markers of a lineage are found in a cell, only markers of that lineage are present. Thus, the finding of markers of two lineages in single cells is evidence of abnormal program assembly.

A beginning has been made in testing the relevance of these findings. Evidence of lineage infidelity has been obtained in cells from 9 of 20 patients with acute leukemia. Even for this small series, remission-induced therapy was significantly more successful where doubly-marked cells were not found. Many more patients must be studied but, as in the case of self renewal, the clinical correlation provides evidence for the validity of the laboratory findings.

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*Project 402.

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SEARCH FOR PROGNOSTIC FACTORS IN CLINICALLY-STAGED PATIENTS WITH HODGKIN'S DISEASE*

D. E. BERGSAGEL**, *Toronto, Ontario*

Results of the treatment of 780 primary patients with Hodgkin's disease at the Princess Margaret Hospital (PMH) betwen 1968 and 1977 are analyzed. Treatment decisions were based on the evaluation of the extent of disease by clinical methods. A marked improvement in relapse-free survival and overall survival was observed for 1973-1977 and compared to 1968-1972. This improvement did not result from differences in the distribution of important prognostic attributes (clinical stage, pathology, and age) between the two periods, and there was no improvement in our ability to rescue relapsed patients. Improved relapse-free and overall survival during the second period was observed for all stages in patients <50 years of age, but not in the older group. The improved survival of patients treated between 1973 and 1977 is attributed to more effective initial therapy, which reduced the fraction of patients who relapsed. These observations provide indirect evidence that relapse has a negative effect on prognosis, and that the initial treatment of patients with Hodgkin's disease should be designed to reduce the risk of relapse to a minimum without causing an unacceptable increase in late complications. The observed/expected incidence of acute leukemia and non-Hodgkin's lymphoma in the PMH series was increased to 41.9 and 13.9 respectively. The question of whether a policy of doing routine staging laparotomies improves the results of treatment of patients with Hodgkin's disease is considered only in general terms by comparing the total PMH series with the total Stanford Medical Center series of patients treated between 1968 and 1977. Relapse-free survival at 10 years is 48.9% and 66.8%, respectively, at the two institutions, while overall survival at 10 years is identical.

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*Project 423.

**Chief of Medicine, Princess Margaret Hospital, Toronto; and Professor of Medicine, University of Toronto.

MAMMOGRAPHIC PATTERNS AS INDICATORS OF RISK FACTORS FOR BREAST CANCER*

N. F. BOYD**, B. O'SULLIVAN†, J. E. CAMPBELL‡, E. FISHELL§, I. SIMOR††, G. COOKE‡‡ and T. GERMANSON,§§ *Toronto, Ontario*

We have carried out a case control study to examine the relationship between mammographic signs and breast cancer. The mammographic signs assessed were those of prominent ducts and dysplasia.

The cases in this study were 183 women with histologically verified, unilateral breast cancer. The controls were a group of women attending a screening centre. Cases and controls were individually age matched. Mammograms for the non-cancerous breast of the cases were assembled randomly with those of the controls, and classified by three radiologists without knowledge of which films were from cases and which from controls.

Mammographic dysplasia was found to have a strong association with breast cancer, particularly in women aged less than 50. Prominent ducts were only weakly associated with breast cancer. Multivariate analysis showed that the association between dysplasia and breast cancer could not be explained on the basis of other risk factors for breast cancer, and that classification of dysplasia discriminated more strongly between cases and controls than did classification of Wolfe's mammographic patterns.

These results show that the mammogram contains information about the individual's risk of developing breast cancer. Unlike other risk factors, mammographic dysplasia has a strong association with breast cancer, is present in a substantial proportion of patients with the disease, and may offer opportunities for prevention.

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*Project 424.

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‡Clinical Trials Secretary, PMH.

§Assistant Chief Radiologist, Women's College Hospital, Toronto.

††Radiologist, Mount Sinai Hospital, Toronto; and Assistant Professor of Radiology, U of T.

‡‡Radiologist, St. Michael's Hospital, Toronto; and Assistant Professor of Radiology, U of T.

§§Statistician, Department of Biostatistics, OCI.

CLASSIFICATION OF SURVIVAL CURVES*

A. CIAMPI**, *Toronto, Ontario*

We are developing a methodology and a computer software package for the classification of survival curves into classes defined directly in clinical terms. Given a series of patients for which prognostic factors and survival data are recorded, the aim is to subdivide it into subpopulations, characterized by simple statements involving prognostic factors, such that their survival curves are optimally separated.

So far, we have been studying a "recursive partition" algorithm and its variants, based on pairwise comparisons of survival curves, and we have tested it on several data sets of clinical significance. Also, the same data sets have been analyzed by regression models in order to compare the performance of our classification strategy with more conventional methods of analyzing survival data. The results seem encouraging.

In order to deal with more specific features of the survival curves which occur in oncology, and in order to define "optimal" separation among curves, we have investigated the validity of the "proportional hazards" assumption, and we have developed new parametric and semi-parametric regression models which are not necessarily based on that assumption.

Work in progress includes efforts to refine computational techniques, to improve efficiency in the recursive partition algorithm, and to develop other classification strategies based on clustering techniques.

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*Project 426.

**Senior Scientist, Ontario Cancer Institute, Toronto.

CLINICAL TRIALS SECRETARY FOR GASTROINTESTINAL TUMOR GROUP*

B. J. CUMMINGS**, *Toronto, Ontario*

In Ontario, approximately 70 patients per 100,000 population develop malignant tumors of gastrointestinal tract and 700 new patients with such tumors are referred to the Princess Margaret Hospital each year. Secretarial assistance is provided under this project for studies on subgroups of these patients.

A prospective Phase I-II study of high-dose intravenous infusion of 5-fluorouracil with allopurinal was performed in 50 patients with metastatic colorectal carcinoma. Although higher does of 5-fluorouracil than usual could be given, the response rate remained less than 20%, and no improvement in therapeutic efficacy over 5-fluorouracil alone was demonstrated[1].

The results of primary radiation therapy for patients with rectal adenocarcinoma treated during the period from 1970 to 1977 were reviewed. Most of these patients either were unsuitable for surgical treatment or had refused surgical procedures which required a colostomy. The overall five-year survival rate was 21%, 38% for those with clinically mobile tumors, and 2% for those with fixed tumors[2].

Prospective studies of postoperative and preoperative adjuvant therapy for patients with rectal carcinoma have continued.

Further experience with combined 5-fluorouracil, mitomycin C and radiation therapy for patients with anal-canal carcinoma has confirmed that this combination is effective in controlling these tumors, so that surgery can be reserved for those patients with residual carcinoma[3]. A Phase I study of this combination therapy now is underway in patients with squamous-cell carcinoma of the esophagus.

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*Project 427.

**Radiation Oncologist, Princess Margaret Hospital, Toronto; and Associate Professor of Radiology, University of Toronto.

EVALUATION OF NEW ULTRASOUND DIAGNOSTIC SYSTEMS TO DETECT AND CHARACTERIZE BREAST NEOPLASMS*

J. W. HUNT**, F. S. FOSTER† and E. FISHELL‡
Toronto, Ontario

The early detection of breast cancer by means of safe effective diagnostic techniques is an important component of the overall effort to reduce the mortality of this disease. Our goal has been to develop new ultrasonic breast imaging techniques and evaluate these in the breast clinic. One system, called the annular array scanner, has been completed and during the past year has undergone evaluation at Women's College Hopsital. This system scans automatically, generating high-quality, tomographic slices of the breast separated by as little as 2 mm and covers the whole breast and the axilla. Over the past year, 97 symptomatic patients were examined in an effort to learn the ultrasonic characteristics of breast lesions and to determine the strengths and weaknesses of our scanner. This study has confirmed our ability to observe a wide range of breast abnormalities with good definition. One of the principle difficulties with the instrument was the long time required for patient examination (~ 1 hr). We have carried out extensive modification of the system so that a complex examination now takes less than 20 minutes. Rigorous clinical evaluations of a comparison of x and ultrasound mammography have begun in September 1982.

A new scanner with a unique conical geometry, which was invented at the Ontario Cancer Institute, has undergone a rapid development this year. This hybrid scanner consists of an annular array (as the ultrasound transmitter), and the conically-shaped transducer (as the receiver). The effective lateral resolution is better than 1 mm over all depths of the breast. This design provides exceptional acoustic images of the breast. Based on this success, both the OCI and a commercial organization are completing two clinical prototypes based on this system, and we hope that clinical trials at the Women's College Hospital will begin in the near future.

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*Project 428. (Continuation of Project 400)

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‡Associate Radiologist-in-Chief, Women's College Hospital, Toronto; and Lecturer in Radiology, U of T.

IMMUNOLOGIC PROBES OF DRUG RESISTANCE IN HUMAN TUMOR CELLS*

G. B. PRICE**, *Toronto, Ontario*

Cells selected for resistance to vinca-alkaloids or antitumor antibiotics show striking similarities in their resistance mechanisms. This common mechanism is the acquisition of an energy-dependent permeability barrier in the plasma membrane[1,2]; this barrier to the selecting drug has been shown to result in collateral resistance to other cytotoxic drugs. This barrier has been associated with a "novel" membrane glycoprotein with a molecular weight of 170,000 to 190,000 daltons[3]. We have produced two mouse monoclonal antibodies, which specifically recognize drug-resistant cell lines of this type[4]. Preliminary experiments have shown that one monoclonal antibody can recognize an antigen of apparent molecular weight, 180,000 daltons. In addition, one human monoclonal antibody[5], which specifically labels drug-resistant mutant cell lines but not the drug-sensitive parental lines, is under continuing investigation. We anticipate that the use of these monoclonal antibodies in prospective studies of clinical relevance and correlation will confirm their usefulness. Retrospective studies of cells from drug-resistant tumors of patients, with one of the monoclonal antibodies, suggest that prospective studies will provide criteria for the application of this monoclonal antibody to the prediction of responses to various chemotherapy regimens. Successful clinical studies should also provide a clearer perspective with respect to any immunotherapic role for these antibodies.

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*Project 429. (Final Report)

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CLINICAL TRIALS IN BREAST CANCER*

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Toronto, Ontario

Four randomized controlled clinical trials are now in progress.
These are:

1. A randomized controlled trial of ovarian irradiation and prednisone, following operation and radiotherapy, was undertaken for carcinoma of the breast. This trial compared three forms of adjuvant therapy: ovarian irradiation and prednisone; ovarian irradiation alone; and no further treatment. There have been 756 patients enrolled and they now have been followed for at least eight years. In premenopausal women, aged 45 years of more, ovarian irradiation and prednisone significantly delayed recurrence, and prolonged survival. Further follow-up and analysis continue.
2. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in premenopausal patients with histologically involved axillary nodes. This trial compares two treatment modalities: (a) combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF), and ovarian irradiation plus prednisone; and (b) CMF alone. The trial is designed to determine if chemotherapy and hormonal therapy are complementary. To date, 131 patients have been enrolled.
3. A randomized controlled trial of postoperative treatment of breast cancer is being conducted in postmenopausal patients with histologically involved axillary nodes. No currently available adjuvant therapy is known to benefit this group of patients and this trial examines the usefulness of tamoxifen as an adjuvant agent. To date, 306 patients have been enrolled.
4. In a Phase II trial, the value of tamoxifen in the treatment of metastatic breast cancer in premenopausal women is being studied. Of 53 evaluable patients, 4 have had complete responses (CR) and 10 partial responses (PR). Six patients have remained stable (ST) on treatment. The response rate (26% for CR + PR; 38% for

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*Project 446, including Projects 378 and 386.

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CR + PR + ST) and the response duration (13+ months) seen in this study suggest that tamoxifen may achieve an effect comparable to that of ovarian ablation in premenopausal women with metastatic breast cancer. The study has also shown that steroid receptors generally were predictive of response to tamoxifen, and that tamoxifen response was highly predictive of response to subsequent ovarian ablation. A follow-up study comparing tamoxifen to ovarian ablation in a prospective randomized fashion is being planned with the support of the National Cancer Institute of Canada.

PHASE III CLINICAL TRIAL OF MISONIDAZOLE AND RADIATION THERAPY*

G. M. THOMAS**, A. M. RAUTH†, B. J. CUMMINGS‡ and R. S. BUSH††,
Toronto, Ontario

One of the reasons for failure to control tumors locally with radiation may be the presence of hypoxic cells which are relatively radioresistant. The chemical compound, misonidazole, has been shown in vitro and in vivo experimental studies to sensitize hypoxic cells to the effects of radiation. As such it may contribute to improved radiation control and cure of human carcinomas. This study will explore whether the addition of misonidazole to a conventional course of radiation therapy can improve local control rates and cure rates for patients with carcinoma of the cervix. Our previous toxicity study of misonidazole and radiation has established that the daily dose of misonidazole, which can be administered safely (with acceptable toxicity), is 0.45 g/M^2 for 22 treatment days – a total of 9.9 g/M^2. At this dose the limiting toxicity was a sensory peripheral neuropathy.

Patients with carcinoma of the cervix with bulky disease confined to the cervix or with more extensive pelvic disease are randomized, double blind, to receive either standard pelvic irradiation with placebo capsules, or to receive the same radiation with misonidazole capsules. This study has been accruing patients since October 1981. Efficacy results will not be available until sufficient patients have been entered into the study and followed for adequate periods to determine the outcome of treatment.

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*Project 448.

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CHROMOSOME STUDIES IN RETINOBLASTOMA*

H. A. GARDNER**, *Toronto, Ontario*

The two-step, gene-mutation theory of Knudson attributes familial retinoblastoma to a prezygotic mutation carried in every cell in the body. Although the retina may appear to be most susceptible to a second tumorogenic insult, the lymphocyte may reveal evidence of this first germ-cell mutation.

In our experiments, a mixed lymphocyte culture of subjects of the opposite sex is used as a critical control. Preliminary testing, using chromosome instability as a probe, has failed to show any change in chromatic and chromosome breaks, gaps, rearrangements, or sister chromatid exchanges. These studies were done in unchallenged culture. The next phase of this study is to challenge lymphocytes with clastogenic agents such as mitomycin C, looking for evidence of an enhanced susceptibility to chromosome damage.

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*Project 411.

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University of Toronto

HORMONAL CONTROL OF PROSTATIC CANCER*

B. G. MOBBS**, *Toronto, Ontario*

In an on-going study of the basic mechanisms involved in the hormonal control of prostatic disease, we have continued to investigate the quantity and cellular distribution of androgen receptor (AR) protein in benign and malignant prostatic tissue. The proportion of cytosol AR occupied by endogenous androgen at the time of biopsy is also quantitated. Wide variations in AR content, distribution and occupancy were observed in both benign prostatic hypertrophi (BPH) and carcinoma tissue. In BPH tissue obtained at open operation, mean values (±S.D.) for total cell AR, per cent of total cell AR in the nucleus, and per cent of cytosol AR occupied by endogenous androgens were 1110 ± 531 fm (10^{-15} moles) per mg DNA, 35 ± 17% and 82 ± 13% respectively. The corresponding values for BPH tissue obtained by transurethral prostatectomy (TURP) were 690 ± 217 fm/mg DNA, 37 ± 20% and 88 ± 11% respectively. In carcinoma specimens consisting of ≤70% malignant tissue taken from untreated patients (open and TURP specimens), the corresponding values were 70 ± 457 fm/mg DNA, 29 ± 14% and 73 ± 29%.

In carcinoma patients, treated with estrogens and/or orchiectomy in order to depress serum testosterone levels, the cellular distribution of AR was markedly different. In orchiectomized patients, total cellular AR content was 241 ± 81 fm.mg DNA, of which only 19 ± 26% was found in the nucleus (<100 fm/mg DNA, in all cases). The amount of cytosol AR bound by endogenous androgen was 86 ± 102 fm/mg DNA (42 ± 33%). In estrogen-treated patients, nuclear AR concentration and the proportion of bound cytosol AR were similarly reduced, but total cytosol AR concentrations were similar to those in untreated patients. In patients who were orchiectomized and estrogen treated, cytosol AR concentrations were extremely high (3740 ± 1475 fm/mg DNA) and, in three of these, nuclear AR concentrations were >130 fm/mg DNA, i.e., similar to concentrations observed in untreated patients. This phenomenon may be a significant factor in relapse of patients with advanced prostatic cancer from control by hormone treatment, and this possibility is under further investigation.

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*Project 251.

**Associate Professor of Surgery (Research), University of Toronto.

EVALUATION OF SCREENING FOR CARCINOMA OF THE CERVIX*

E. A. CLARKE**, *Toronto, Ontario* and
T. W. ANDERSON†, *Vancouver, B.C.*

This is the final report of a case-control study which demonstrated the following:

- A three-fold reduction in risk of developing cervical cancer in women who had a Pap smear in the absence of symptoms in the previous five years.
- In this time interval, women who had smears, which showed mild dysplasia, had a four-fold increase in risk of developing cervical cancer, and those with moderate dysplasia were at 62 times the risk of developing cervical cancer. These women with abnormal smears who subsequently developed cancer either did not return for repeat smears, were considered to be false positive because the subsequent smears were negative, or were not referred for treatment for a variety of reasons.
- Women had a two-fold increase in risk of developing cervical cancer if they were current smokers. This significant effect of smoking was not diminished by simultaneously adjusting for age, education and indices of sexual behaviour.
- A greater proportion of cases, 50%, had evidence of previous infection with herpes virus compared to 35% of controls.
- The "interval" sojourn time was calculated in months from the date of the last normal smear to the date of the diagnosis of the case. Controls were given the same date of diagnosis as their matched index case. The trends in risk ratio indicated a protective effect of a single normal screening Pap smear in a period of 36 months. These data will be used in a collaborative evaluation of screening programs with the International Agency for Research on Cancer.

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*Project 302. (Final Report).

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†Head, Department of Health Care and Epidemiology, University of British Columbia, Vancouver, B.C.

THE IRRADIATED LARYNX AND VOICE*

M. L. STOICHEFF** and J. M. FREDRICKSON†, *Toronto, Ontario*

At specified time intervals, tape recordings of a standard reading passage were made of 48 male patients with laryngeal cancer who had received 5000 rads in 20 treatments over a period of four weeks at the Princess Margaret Hospital. Aerodynamic measures were obtained. Information concerning smoking, alcohol intake and vocal usages were elicited on each occasion. The same measures and information were obtained from a control group.

The first analysis is concerned with the perceived voice of the irradiated patients. Interval scaling of the severity of perceived dysphonia was completed for voices of male patients sampled before and one year after radiation therapy, and for a set of male controls. Eight listeners did this quantitative rating and also specified the predominant quality in each voice. The results indicated that the degree of dysphonia was highest in the pretreatment group. Radiotherapy decreased this dysphonia but not to the point that post-treatment voices were indistinguishable from those of normal subjects. Also, the voice qualities of laryngeal cancer patients shifted toward those of the control group following radiotherapy: Over one-half of the irradiated patients judged to have rough or normal qualities.

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*Project 323.

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RESEARCH UNIT OF THE DIVISION OF EPIDEMIOLOGY AND STATISTICS OF THE ONTARIO CANCER TREATMENT AND RESEARCH FOUNDATION*

E. A. CLARKE**, R. F. SPENGLER†, C. L. SOSKOLNE†† and N. KREIGER‡
Toronto, Ontario

Since 1978, a research unit of the division has been operating in the Department of Preventive Medicine and Biostatistics at the University of Toronto. The unit was established to conduct analyses using the cancer data base of the Foundation, to assess the quality of the cancer data base, to co-operate with cancer researchers by providing epidemiological and statistical assistance, to conduct or support cancer research projects, and to provide information, which will improve the knowledge of the general public and scientific community. Many projects have been undertaken in these areas and examples are presented below.

Analysis of Data Base

The mortality data base is used continually to assess experience for various areas within Ontario where there has been community concern regarding environmental carcinogens; these have included Stouffville and Niagara-on-the-Lake. The effects of urea formaldehyde on the general public is a current issue. Focussing on the occupational groups most likely to be exposed to formaldehyde, the Ontario mortality from 1972 to 1979 was analysed. No cancer of the nasal cavity was found to be the cause of death in any physicians, dentists, morticians or non-medical anatomists and pathologists in this time period. If there is a risk of nasal cancer associated with formaldehyde exposure, it is probably small.

Data Quality

A detailed review of 791 cases of cancer of the cervix was performed on newly diagnosed and registered cases in Ontario in 1971. At the time of registration, pathology reports were not available for the compilation of incidence data, and these were requested. Of the 304 cases registered by hospital reports per se, in only 94

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*Project 381.

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‡Epidemiologist/Biostatistician, OCTRF; and Assistant Professor of Preventive Medicine, U of T.

(31%) was the diagnosis of invasive cancer confirmed by the pathology report. Of the remaining 210 cases registered by hospital reports alone, the majority of cases were diagnosed as having carcinoma of the cervix in situ and non-malignant lesions of the cervix such as chronic cervicitis. The crude rate of invasive carcinoma using this revised information was 14.9 per 100,000 in 1971 compared to the original reported figure of 19.9. This indicates the value of pathology reports in the use of multiple sources in registering new cases of cancer in a population.

Co-operation with Researchers

The Research Unit assisted the clinical staff of the Windsor Clinic in an analysis of Stage II patients with breast cancer treated with a combination of radiotherapy and chemotherapy. Recurrence, morbidity and survival rates were calculated.

The Research Unit, in conjunction with the Canadian Association of Dermatologists, determined the prevalence of mycosis fungoides in Canada. Eighty-six cases have been identified in the three-year period (1979-1981). This information will be used by the Association in determining the feasibility of further studies of this rare tumor.

Assistance is being given to researchers in the Toronto area in the analysis of data. Two of these projects should be completed within the current year. One is an evaluation of the effects of cryosurgery in precancerous lesions of cancer of the cervix, and the other an evaluation of risk factors for breast cancer in a cohort of 4130 women followed for at least 20 years by Women's College Hospital.

Internationally, the Research Unit is continuing its collaboration with the Drug Epidemiology Unit of the Boston School of Medicine. A case-control study in Toronto using neighbourhood controls is already in progress, exploring the hypothesis that oral contraceptives, supplemental female hormones, diazepam, reserpine, alcohol and diet affect the risk of developing cancer of the breast. It is anticipated that data will be obtained on 200 newly diagnosed cases of breast cancer, the majority of whom will be patients at the Princess Margaret Hospital, together with information on 400 age-matched neighbourhood controls.

The Research Unit is continuing its collaboration with the International Agency for Research on Cancer which Canada has recently joined. The Research Unit contributed data to the cohort study for the International Radiation Study of Cervical Cancer. Identification of cases and controls within this cohort is being undertaken. Information regarding dosimetry as well as risk factors for the different types of cancer are being studied. It is hoped that this case-control approach will provide additional information about the effects of low-dose irradiation and the occurrence of second, primary malignancies.

Research

The unit has reviewed cancer mortality in occupational groups in Ontario between 1973 and 1979. Some 80 occupational groups have been evaluated using a proportionate mortality ratio (PMR) analysis. The unit also has completed the analysis of a

case-control study in endometrial hyperplasia. Endometrial hyperplasia was strongly associated with the use of exogenous estrogens. Different measures of obesity did not show a significant association. Furthermore, the principal investigators are completing research projects supported by grants from the Foundation, which are reported elsewhere in this volume.

Future Direction

The unit will continue with its program and intends to add more detailed investigation into occupational and environmental factors. In addition, time trends in female genital and childhood cancers will be assessed.

RETINOBLASTOMA AS A MODEL FOR TUMOR-HOST INTERACTIONS*

B. L. GALLIE**, *Toronto, Ontario*

Some of the children who develop retinoblastoma (RB) are predisposed to multiple retinal tumors, which develop in infancy, because of an autosomal, dominantly inherited trait. At later ages, the susceptible cell — the retinoblast — matures and is no longer at risk for malignant transformation. However, individuals with the RB gene continue to carry a markedly increased risk of developing other kinds of malignancies.

Enzyme (esterase D) linkage studies in a large family, done in collaboration with R. Payne of Newfoundland, have shown that the RB gene is located on chromosome 13q14. One individual, who was predicted to be an RB gene carrier on the basis of enzyme studies, but did not have RB, was found to have a retinoma — a benign retinal manifestation of the RB gene, which we defined after a study of 32 patients. We propose that retinoma develops when malignant transformation occurs before terminal differentiation in an intermediate phase of maturation of retinoblasts.

In separate studies we observed that growth properties of fibroblasts in tissue culture are controlled by genetic factors, which vary with age — fibroblasts from younger individuals grow more readily than those from adults. Although the difference is not sufficient to allow detection of the RB gene, patients with this gene show a rate of change in fibroblast growth properties with age, which is different from that of normal persons. This observation reinforces the idea that the mechanism for tumor predisposition by the RB gene may be alteration in cellular maturation.

The RB gene is not sufficient to cause malignancy because, of all the cells at risk, only a few become malignant. Our studies of tumor karyotype rearrangements suggest that chromosome 13 may not be specifically involved at the level of malignant transformation. Instead, one or both of two specific chromosome rearrangements were observed in every tumor: triplication of chromosome 1q or isochromosome 6p. Isochromosome 6p has not previously been described, and my be unique to RB tumors.

Thus, data are accumulating to suggest the following hypothesis: The RB gene on 13q14 predisposes to tumor formation by altering the maturation of retinoblasts and other cells, resulting in a period of susceptibility to malignant transformation. The genetic events resulting in malignant transformation may involve other regions of the genome, such as chromosome 1q or 6p.

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*Project 399.

**Associate Professor of Ophthalmology, University of Toronto.

CONSTRUCTION AND TESTING OF CODED-APERTURE COLLIMATION SYSTEMS FOR GAMMA-RAY CAMERAS*

M. L. G. JOY**, *Toronto, Ontario*

The purpose of this research is to construct and test a novel, relatively inexpensive, tomographic imaging system for use in nuclear medicine. The system being investigated is called Fourier multiaperture emission tomography (FMET)[1]. Physically it is a collimator, which is mounted on a gamma camera like a regular collimator. The FMET collimator allows the positioning of any one of a number (now 32) of coded-aperture plates in front of the camera. The coded images produced by these plates are processed digitally to form a series of tomographic "slices" in planes parallel to the camera. The thickness of these slices increases with depth but is about 1.5 cm at 10 cm from the plate. The resolution in the plane is about 8 mm. Currently, 10 to 20 minutes is required for the acquisition of the coded images.

In the past year the computer programs used in the processing have been revised. The processing time has been reduced from 1½ hours to under 10 minutes. This has allowed us to complete our measurements of the quantum noise performance of the system. Currently we are analyzing these data so that they can be compared with the theory we have developed[2]. This comparison will determine whether we can expect any improvement in the performance of this instrument.

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*Project 413.

**Associate Professor, Institute of Biomedical Engineering and Department of Electrical Engineering, University of Toronto.

EPIDEMIOLOGY OF CERVICAL DYSPLASIA*

E. A. CLARKE** and G. LICKRISH†, *Toronto, Ontario*

Information on risk factors associated with cervical dysplasia, and detailed smoking and "Pap" smear histories have been collected from 250 cases and 500 controls matched by age and neighbourhood. Cases were women residents of Toronto and Mississauga between the ages of 20 and 59 with histological diagnoses of cervical dysplasia, seen at the Dysplasia Clinic of Toronto General Hospital. Collection of data from physicians on prior "Pap" smears for both cases and controls is nearing completion.

Analysis to date has indicated that cases and controls are similar with regard to age at menarche and number of pregnancies; however cases are significantly younger than controls with regard to age at first intercourse (18 vs 19). Cases also have a greater number of sexual partners (4 vs 2) and more years of oral contraceptive use (5 vs 3). Fewer cases than controls have completed high school (54% vs 64%). After simultaneous adjustment for the above factors, there are significantly more current smokers among the cases than the controls (66% vs 40%) giving a relative risk of 1.9 compared to women who never smoked.

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*Project 414.

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ENDOSCOPIC PHOTOGRAPHY OF THE VASCULATURE OF RECURRENT SUPERFICIAL BLADDER TUMORS*

J. G. CONNOLLY**, *Toronto, Ontario*

Work on this project continues. All of the photography is now being conducted at the Princess Margaret Hospital. We now have good photographic evidence that some non-invasive bladder cancers begin as benign tumors and, at this stage, are totally dependent on their mucosal blood supply. It is at this stage that they are most susceptible to intravesical chemotherapy. Many of these agents are effective by virtue of the fact that they induce edema of the lamina propria with accompanying disruption of the tumor blood supply. However, it appears that, in some patients, a tumor angiogenesic factor persists, which stimulates the development of new bladder cancers.

It is now apparent that the next step in the management of these patients is to select agents which inhibit tumor angiogenesis. There are several such compounds and these will have to be investigated for their possible use in the management of superficial bladder cancer.

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*Project 431.

**Associate Professor of Surgery, University of Toronto; and Head, Department of Urology, Women's College Hospital, Toronto.

EVALUATION OF AN ELECTROMECHANICAL LARYNX*

V. S. DAYAL** and M. L. G. JOY†, *Toronto, Ontario*

Laryngeal cancer accounts for 1.8% of carcinoma seen every year in Ontario. The conventional treatment for these tumors is surgery, radiation or a combination of both. A crude estimate of the number of laryngectomies performed each using data from the Ontario Cancer Treatment and Research Foundation and the American Cancer Society is approximately 284 in Ontario and 8000 in North America. The two main handicaps following a laryngectomy are an often poor voice, i.e., esophageal speech, and a permanent tracheostome. Several devices have been built and procedures developed to improve the quality of voice in these patients. Up to the present none of these has been very successful. In common use is a fistula technique, which creates a fistula between the trachea and pharnyx; this gives a reasonable voice. The main problem with this procedure has been aspiration. We have developed an electromechanical device, which prevents aspiration of liquids and solids into the trachea in the presence of tracheopharyngeal fistula. In experimental animals it permits normal breathing. Dogs undergoing a laryngectomy have worn this device and the longest survival time has been over a year. Cine x-rays of swallowing show that this device is effective in preventing aspiration and chest radiographs over periods of time have not shown any aspiration pneumonitis.

During the period of this grant, part of the proposed research objectives have been realized. These include miniaturization of the device; creation of an alternative source to the use of CO_2 in the power pack for the larynx, and the development of a magnetic air pump; the electromechanical larynx has been redesigned and produced in a smaller size as well; a warning signal for low battery power and low CO_2 volume has been added to make the device still safer; a number of electromechanical larynx are being built for the planned use in patients. A series of five articles were published in *Annals of Otology, Rhinology and Laryngology* 1982, **91** (Supp 95): 1-32.

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*Project 451.

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Women's College Hospital, Toronto

COHORT STUDY OF FACTORS ASSOCIATED WITH THE DEVELOPMENT OF BREAST CANCER*

K. I. PRITCHARD** and M. WYNNE-JONES†
Toronto, Ontario

Initially this project, which was undertaken at Women's College Hospital by Dr. Helen Bell Milburn in 1945, was designed to determine the relationship between breast changes at menstruation, pregnancy, lactation and menopause, and the subsequent development of breast cancer. Between 1956 and 1972, 4152 volunteers were enrolled in the study, including 3156 students from successive nursing classes in Toronto hospitals. Detailed history and physical examination were taken at the time of intitial enrolment and the cohort then was followed at three-year intervals.

As of 1978, 77% of the volunteers (79% of the student-nurse subset) had maintained contact. At that time an intitial analysis was done by Miss Terry Germanson and Dr. E. Aileen Clarke. At that time 80 breast cancers had developed in the total group of volunteers, 32 of those in the student-nurse subset. The analysis directed attention to the student-nurse subset because they were unselected. In this group the development of breast cancer in the 30- to 39-year age group was associated with large breast size, a family history of breast cancer, a family history of benign breast disease and breast changes at the time of menstruation. A report concerning this intitial analysis has been submitted for publication.

In 1979 a further questionnaire was mailed to the entire cohort. Of the cohort 74% (78% of the student-nurse subset) have now been contacted and further information on a number of variables has been collected. The updated information thus obtained has now been computerized and a multivariable analysis is underway.

Initially the information will be analyzed as a case-control study within a cohort. A further standard cohort study analysis is then planned. Current analysis is being supervised by Drs. Gayle Eyssen and Colin Soskolne.

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*Projects 11 and 433.

**Co-Director, Henrietta Banting Breast Cancer Centre, Women's College Hospital, Toronto; Assistant Professor of Medicine, University of Toronto; Consultant in Medical Oncology, Princess Margaret Hospital, Toronto; and Clinical Trials Scholar, National Cancer Institute of Canada.

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EPIDEMIOLOGY AND STATISTICS

CANCER MORTALITY, INCIDENCE AND TREATMENT IN ONTARIO

E. AILEEN CLARKE, M.B., B.S.*, NANCY KREIGER, M.P.H., Ph.D.**
LORAINE D. MARRETT, Ph.D.** and C.L. SOSKOLNE, Ph.D.**
Toronto, Ontario

The Division of Epidemiology and Statistics is responsible for one of the mandates of the Foundation — the adequate reporting of cases and the recording and compilation of data. Towards this objective, the Foundation has maintained and improved the uniform case recording system adopted by the regional treatment centres in 1937. These data are in machine-readable form from 1960 onwards. In addition to these records, the computerized cancer data base of the Foundation contains individual records on residents of Ontario who died from cancer since 1950; tabulations by sex, five-year age group and site of cancer deaths from 1931 to 1981; similar tabulations for incidence data for 1964 to 1966 and 1969 to 1971; individual records of hospital discharges on patients with cancer from 1964 to 1981; pathology reports on specimens of cancer from 1972 to 1981. The total volume of records, in excess of three million, provides the Division with a unique opportunity for descriptive cancer epidemiology and, in spite of the delays in the generation of timely incidence tabulations, allows the Division to assist other cancer researchers in the investigation of possible carcinogenic effects of exposure to occupational and environmental agents.

The Division is fortunate to have recruited to the staff Drs. Kreiger, Marrett and Soskolne as epidemiologists. Most of the Division is located in the Head Office of the Foundation at 7 Overlea Boulevard but Dr. Soskolne, who is responsible for the Research Unit of the Division, is located in the Department of Preventive Medicine and Biostatistics at the Faculty of Medicine of the University of Toronto. This arrangement allows the staff of the Division to interact with other members of the epidemiological community as well as with medical and oncological colleagues. Earlier this year, Dr. Robert Spengler resigned and, at his suggestion, the structure of the Division no longer includes his position — Assistant Head of the Division.

CANCER MORTALITY

For the past year, the Division has been reviewing the data base at the Foundation on mortality in Ontario. Presented here are data from the two ends of the analytic

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spectrum: a close examination of one year (1981), and a review of 51 years (1931-1981), of cancer deaths in the province.

Mortality, 1981

Computerized data on deaths due to all causes in Ontario residents for the year 1981 have been provided by the Office of the Registrar General of Ontario. These data have been used to assess the impact of cancer relative to other causes of death, and to examine the distribution of cancer deaths with respect to site of malignancy and age at death for each sex.

For males, Table I shows that the percentage of deaths which can be attributed to cancer increases steadily from the youngest age group to age 55-74 years and then declines, while the proportion of deaths due to diseases of the circulatory system increases even into the oldest age group. For men over the age of 35 years, malignant neoplasms and diseases of the circulatory system account for the large majority of deaths, while more than 75% of males in the age group 15-34 years die of injuries.

TABLE I

Per Cent Distribution of Major Causes of Death in Males Within Age Groups, Ontario, 1981[1]

CAUSE OF DEATH	ICD9[2] NUMBER	AGE AT DEATH (YEARS)				
		0-14	15-34	35-54	55-74	75+
Malignant neoplasms	140-208	6	8	25	30	19
Diseases of the nervous system	320-389	3	2	2	1	1
Diseases of the circulatory system	390-459	2	6	38	48	56
Diseases of the respiratory system	460-519	3	2	3	6	11
Diseases of the digestive system	520-579	1	1	7	5	3
Congenital anomalies	740-759	25	1	0	0	0
Injury and poisoning	800-999	20	76	19	4	3
Other	Other	40	4	6	6	7
ALL CAUSES		100	100	100	100	100

[1]Omitted are seven males of unrecorded age and two infants of unrecorded sex.

[2]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

Malignant neoplasms account for the largest number of deaths in women 35-54 years, exceeding circulatory disease deaths by more than a factor of two (Table II). As in men, deaths due to diseases of the circulatory system constitute an increasing proportion of deaths with advancing age; nevertheless, in the age group 55-74 years, there are nearly as many deaths due to cancer as due to circulatory diseases. Injuries represent almost one-half of the deaths in women aged 15-34 years.

TABLE II

Per Cent Distribution of Major Causes of Death in Females Within Age Groups, Ontario, 1981[1]

CAUSE OF DEATH	ICD9[2] NUMBER	AGE AT DEATH (YEARS)				
		0-14	15-34	35-54	55-74	75+
Malignant neoplasms	140-208	7	19	47	37	14
Diseases of the nervous system	320-389	4	3	3	2	1
Diseases of the circulatory system	390-459	2	7	20	41	64
Diseases of the respiratory system	460-519	4	4	3	5	7
Diseases of the digestive system	520-579	1	3	6	5	3
Congenital anomalies	740-759	26	3	0	0	0
Injury and poisoning	800-999	18	49	14	3	3
Other	Other	38	12	7	7	8
ALL CAUSES		100	100	100	100	100

[1]Omitted are four females of unrecorded age and two infants of unrecorded sex.

[2]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

Malignant neoplasms of the trachea, bronchus and lung account for most cancer deaths among males (Table III, Fig. 1); the intestine and the prostate are the second and third most frequent sites. Malignancies at each of the major digestive tract sites shown in Table III (esophagus, stomach, intestine, rectum and pancreas) are important causes of death which rank high in comparison to other sites; in fact, almost as many deaths were due to cancers of these sites -- 2102, as were due to cancers of the respiratory tract -- 2711.

TABLE III

Number of Deaths due to Malignant Neoplasms in Males, by Site of Disease and Age at Death, Ontario, 1981

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	–	–	–	–	–	–	1	2	4	8	7	18	16	16	12	27	111	15
Pharynx	146-148	–	–	1	1	1	–	–	1	1	8	7	6	13	9	8	9	65	
Esophagus	150	–	–	–	–	–	–	–	2	4	6	15	25	18	55	33	49	207	10
Stomach	151	–	–	–	–	–	1	2	3	4	9	20	55	56	69	72	134	425	4
Intestine, except rectum	152,153	–	–	–	–	1	3	3	10	11	24	45	73	87	132	126	246	761	2
Rectum and anus	154	–	–	–	–	–	–	1	2	2	15	15	34	36	50	50	105	310	6
Pancreas	157	–	–	–	–	–	–	–	3	5	9	30	42	57	57	85	111	399	5
Nasal cavities, middle ear and accessory sinuses	160	–	–	–	–	–	–	–	–	–	1	–	4	3	2	2	4	16	
Larynx	161	–	–	–	–	–	–	1	1	2	2	9	15	23	28	12	22	115	14
Trachea, bronchus and lung	162	–	–	–	1	–	–	6	7	31	83	198	311	434	450	430	629	2560	1
Bone	170	–	–	1	3	5	2	–	1	1	1	2	1	2	–	2	4	25	
Connective tissue	171	–	2	–	–	–	1	1	2	2	2	2	3	2	2	5	3	27	
Malignant melanoma	172	–	–	–	–	3	3	9	6	10	10	14	14	8	13	8	10	108	16
Breast	175	–	–	–	–	–	–	–	–	–	1	–	4	2	2	4	2	15	
Prostate	185	–	–	–	–	–	–	–	–	–	2	6	16	53	81	127	463	748	3
Testis	186	–	–	–	1	4	4	–	2	1	–	2	1	–	1	2	2	20	
Bladder	188	–	–	–	1	–	–	–	1	1	2	10	19	13	49	51	139	286	8
Kidney and ureter	189.0-189.2	1	2	–	–	1	–	–	–	6	7	18	30	22	30	28	34	179	11
Brain and other nervous system	191,192	4	–	7	2	3	3	9	6	6	20	29	33	21	37	24	20	224	9
Thyroid gland	193	–	–	–	–	–	–	–	–	1	–	1	1	1	2	2	2	10	
Lymphosarcoma and reticulosarcoma	200	–	–	1	3	2	–	2	2	2	7	4	10	10	10	10	17	75	
Hodgkin's disease	201	–	–	–	–	1	3	2	4	2	2	3	6	8	9	5	7	52	
Other lymphomas	202	1	1	1	2	2	2	4	2	2	9	8	21	21	15	29	49	169	12
Multiple myeloma	203	–	–	–	–	–	–	–	–	1	7	6	14	9	17	23	50	127	13
Leukemia	204-208	6	6	6	5	6	3	7	8	5	16	14	18	31	45	49	78	305	7
Other and non-specific	Residual	8	3	3	2	3	3	4	6	15	20	37	73	96	115	109	236	713	
TOTAL	140-208[3]	20	14	20	21	32	28	52	71	119	271	502	847	1042	1296	1308	2427	8070	

[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2]Rank order for sites with more than 100 deaths.

[3]Omitted are 23 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

Fig. 1 Number of deaths due to malignant neoplasms for frequent sites, by sex, Ontario, 1981.

Breast cancer is the most frequent cancer cause of death in females (Table IV and Fig. 1). Approximately one third as many females as males died of cancer of the trachea, bronchus and lung — the second ranking site in females. As for males, malignancies at each of the digestive sites, with the exception of the esophagus, are important causes of death; the five digestive tract sites shown in Table IV account for a total of 1835 deaths; this exceeds the number for breast or respiratory tract cancers. Cancer of the ovary ranks fourth and caused more deaths than cancer of the cervix uteri and "other uterus" combined.

TABLE IV

Number of Deaths due to Malignant Neoplasms in Females, by Site of Disease and Age at Death, Ontario, 1981

SITE OF DISEASE	ICD9[1] NUMBER	AGE AT DEATH (YEARS)																RANK[2]
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75+	All Ages	
Lip and oral cavity	140-145	–	–	–	–	1	–	–	–	–	2	7	7	3	8	4	16	48	
Pharynx	146-148	1	–	–	–	–	–	–	1	–	–	5	6	6	5	3	3	30	
Esophagus	150	–	–	–	–	–	–	–	1	–	–	4	8	13	8	16	30	80	
Stomach	151	–	–	–	–	1	4	3	1	2	9	9	17	23	39	45	107	318	6
Intestine, except rectum	152,153	–	–	1	–	–	2	–	5	9	20	49	71	83	110	123	331	824	3
Rectum and anus	154	–	–	–	–	–	–	–	2	2	9	14	19	24	27	26	110	233	8
Pancreas	157	–	–	–	–	–	–	1	–	3	10	25	31	36	63	60	151	380	5
Nasal cavities, middle ear and accessory sinuses	160	–	–	–	–	–	–	–	–	–	–	–	–	–	3	3	2	8	
Larynx	161	–	–	–	–	–	1	–	–	1	1	5	3	3	5	5	5	29	
Trachea, bronchus and lung	162	–	–	–	–	–	1	3	3	26	45	90	117	177	125	105	150	831	2
Bone	170	–	1	1	2	–	–	–	–	1	–	–	2	1	–	1	3	12	
Connective tissue	171	–	–	–	1	1	–	1	–	1	1	3	1	3	4	1	4	21	
Malignant melanoma	172	–	–	–	–	1	4	4	7	6	6	9	5	7	7	4	10	66	
Breast	174	–	–	–	–	1	7	14	47	66	103	137	177	180	152	150	360	1395	1
Cervix uteri	180	–	–	–	–	1	–	3	9	13	11	17	17	30	19	20	37	180	10
Other uterus	179,181,182	–	–	–	–	–	–	1	1	4	5	5	13	17	23	32	63	164	11
Ovary	183.0	–	–	1	2	2	–	1	4	9	19	46	50	67	64	60	92	421	4
Bladder	188	–	–	–	–	–	–	–	–	–	3	2	6	14	12	14	73	124	13
Kidney and ureter	189.0-189.2	1	1	–	1	–	1	1	2	4	6	9	14	13	28	14	31	122	14
Brain and other nervous system	191,192	3	4	1	3	2	3	4	8	6	14	9	24	25	31	25	21	183[3]	9
Thyroid gland	193	–	–	–	–	–	1	–	–	–	1	1	1	4	3	5	12	28	
Lymphosarcoma and reticulosarcoma	200	–	–	1	–	2	–	1	–	–	–	2	6	5	4	11	23	55	
Hodgkin's disease	201	–	–	–	1	4	1	2	1	1	2	1	2	4	2	2	3	26	
Other lymphomas	202	2	–	1	1	–	–	2	2	4	9	9	10	12	14	16	59	141	12
Multiple myeloma	203	–	–	–	–	–	–	1	–	2	1	2	11	13	16	19	40	105	15
Leukemia	204-208	4	3	7	3	2	6	7	6	7	7	15	21	16	15	37	89	247	7
Other and non-specific	Residual	5	3	3	2	2	3	4	3	7	8	29	68	75	96	112	348	760	
TOTAL	140-208[4]	16	14	16	16	20	37	53	98	172	280	503	713	934	877	969	2255	6831	

[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

[2]Rank order for sites with more than 100 deaths.

[3]Omitted are 12 deaths due to non-melanotic cancer of the skin (ICD9 number 173).

[4]Omitted is one female of unrecorded age.

This is the first year that pancreatic cancer has been reported separately from other digestive cancers. It is interesting to note (from the last column of Tables III and IV) that it ranks fifth as a cause of cancer mortality in both sexes.

Table V gives the 1981 census population of Ontario by sex and age group to permit readers, if they so desire, to compute rates from data in Tables III and IV.

TABLE V

Population of Ontario, by Sex and Age Group, 1981*
(in Thousands)

AGE GROUP	MALE		FEMALE		TOTAL	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
0-4	303.7	7.2	289.3	6.6	593.0	6.9
5-9	317.3	7.5	300.0	6.9	617.3	7.2
10-14	346.7	8.2	329.7	7.5	676.4	7.8
15-19	413.4	9.7	395.5	9.0	808.9	9.4
20-24	392.7	9.2	397.0	9.1	789.7	9.2
25-29	358.8	8.4	376.0	8.6	734.8	8.5
30-34	357.1	8.4	364.4	8.3	721.5	8.4
35-39	291.5	6.9	289.7	6.6	581.2	6.7
40-44	247.2	5.8	244.7	5.6	491.9	5.7
45-49	236.5	5.6	231.5	5.3	468.0	5.4
50-54	235.5	5.5	233.4	5.3	468.9	5.4
55-59	215.8	5.1	233.1	5.3	448.9	5.2
60-64	168.8	4.0	187.7	4.3	356.5	4.1
65-69	141.1	3.3	164.4	3.8	305.5	3.5
70-74	100.7	2.4	130.3	3.0	231.0	2.7
75+	120.0	2.8	211.7	4.8	331.7	3.9
TOTAL	4,246.8	100.0	4,378.4	100.0	8,625.2	100.0

*Source: Ministry of Treasury and Economics.

Since sites of cancer most often causing death in childhood generally are not important causes in adults and, therefore, do not appear in overall ranking of cancer deaths, Table VI lists the five most common causes of death due to cancer among those under 15 years of age. Although crude mortality rates per 100,000 are very low for all of the sites shown, death at these young ages means many years of life lost. For example, assuming that the average age at death for these children is seven years and that their life expectancy would have been about 74 years, each child loses approximately 67 years of potentially productive life. In 1981, the total potential years of life lost in Ontario due to childhood cancer deaths closely approximates that for males dying from cancer of the intestine, the second ranking site in males.

TABLE VI

Crude Rates of Death Due to Malignant Neoplasms in Children, 0-14 Years Old, for the Five Major Sites, Ontario, 1981

RANK	SITE (ICD9[1] NUMBER)	RATE/100,000
1	Leukemia (204-208)	1.802
2	Adrenal gland (194.0)	1.113
3	Brain and other nervous system (191,192)	1.007
4	Other lymphoma (202)	0.318
5	Kidney and ureter (189.0-189.2)	0.265

[1]ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.

Table VII displays the number of deaths at each cancer site and the percentage of those which came to autopsy. It is clear that the rates of autopsy vary greatly with the site of malignancy, ranging from 7% of prostatic cancer deaths to 30% of those due to lymphosarcoma.

TABLE VII

Number of Deaths Due to Malignant Neoplasms and Per Cent Autopsied, by Site of Disease, Ontario, 1981

SITE OF DISEASE	ICD9[1] NUMBER	NUMBER OF DEATHS	PER CENT AUTOPSIED
Lip and oral cavity	140-145	159	8.8
Pharynx	146-148	95	18.9
Esophagus	150	287	11.8
Stomach	151	743	11.3
Intestine, except rectum	152,153	1,585[3]	9.8
Rectum and anus	154	543	7.7
Pancreas	157	779[3]	16.7
Nasal cavities, middle ear and accessory sinuses	160	24	8.3
Larynx	161	144	17.4
Trachea, bronchus and lung	162	3,411	13.1
Bone	170	37	21.6
Connective tissue	171	48	16.7
Malignant melanoma	172	174	17.2
Breast	174,175	1,410	11.1
Cervix uteri	180	180	12.8
Other uterus	179,181,182	164	9.1
Ovary	183.0	421	12.8
Prostate	185	748	6.8
Testis	186	20	20.0
Bladder	188	410	9.5
Kidney and ureter	189.0-189.2	301	14.9
Brain and other nervous system	191,192	408	19.1
Thyroid gland	193	38	21.1
Lymphosarcoma and reticulosarcoma	200	130	30.0
Hodgkin's disease	201	78	21.8
Other lymphomas	202	310	27.4
Multiple myeloma	203	232	13.8
Leukemia	204-208	550	20.7
Other and non-specific	Residual	1,473	12.4
TOTAL	140-208[2]	14,902	13.0

[1] ICD9: International Classification of Diseases, Ninth Revision, World Health Organization, Geneva, 1977.
[2] Omitted are 35 deaths due to non-melanotic cancer of the skin (ICD9 number 173).
[3] Omitted is one death at this site with unrecorded autopsy status.

Mortality Trends

Cancer mortality statistics from 1931 were maintained at the Foundation by Dr. A. H. Sellers, who had standardized the coding of site of cancer over five revisions of the International Classification of Diseases (ICD). In the summer of 1982, Dr. Peter Boyle, of the West of Scotland Cancer Surveillance Unit in Glasgow, visited the Division during his tenure as an IARC Research Training Fellow, and assisted in the computerization of the data, thus enabling us to present age-adjusted cancer mortality trends from 1931 to 1981 (Fig. 2). When comparable codes did not exist in the earlier years, certain sites are presented only for more recent time periods. It should be noted that cancers of all respiratory tract sites, other than larynx, are included in the lung cancer mortality rates shown in Fig. 2, although the majority of the deaths are in fact attributable to lung cancer. All rates are standardized to the 1956 Ontario population and are five-year averages, except for 1981, which is based on a single year of data. The cancer sites have been selected for their current scientific and social interest.

While total cancer mortality for females has steadily declined since 1931, that for males has shown a consistent upward trend. Before 1951, cancer mortality was higher in females than males; since then, the reverse is true. Increasing lung cancer mortality is the predominant explanation for rising overall cancer mortality in men. In females, declining rates of stomach, colorectal and uterine cancer have more than compensated for increasing lung cancer. Lung cancer mortality in males has increased since 1931; in contrast, the increase in women did not begin until 1956-60.

Colorectal cancer, currently the second most common cause of death in both sexes, declined by nearly 30% in females since 1941 but showed no change in males. In women, malignancies of the breast have remained the most frequent cause of cancer death and the rates have not changed. For both sexes, stomach cancer rates have declined by about 70%. Mortality from pancreatic cancer appears to have increased while cancer of the biliary passages and liver has declined. The trends for these latter two sites may be real or may be related to changes in coding or diagnostic practice over time. Cancer of the kidney increased in males with a doubling of the rate over the time period, while remaining constant in females. In both sexes, an approximate two-fold increase is evident over the time period for "other lymphatic" sites. In the coming year, the Division plans to analyze these data using age-period-cohort modelling.

CANCER INCIDENCE

During the past year, working with the Division of Information Systems, and with advice from Dr. G. R. Howe of the National Cancer Institute of Canada Epidemiology Unit and assistance from Statistics Canada, the Division of Epidemiology and Statistics has been developing a record linkage system to produce cancer incidence data for Ontario for the years 1964-1976. The Foundation uses a "passive" reporting system whereby data created on cancer patients for other purposes are linked to produce a unique record on each case of cancer diagnosed each year in the province.

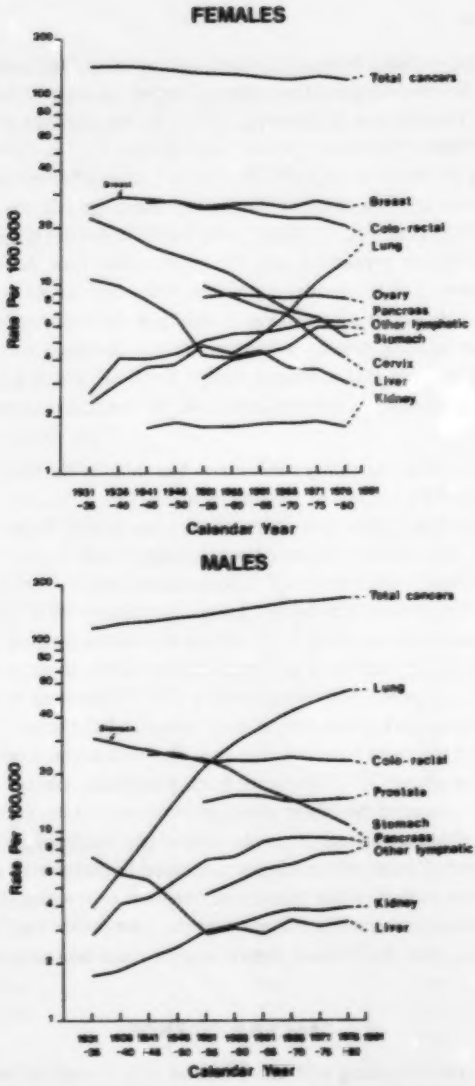

Fig. 2. Age-adjusted mortality trends for selected cancer sites by sex, Ontario 1931-1981. (Age-adjusted to the 1956 census of population of Ontario.)

Different sources of information on cancer patients are received for use in the Ontario Cancer Registry. Each of the source files (Table VIII) is edited, missing data identified and invalid codes corrected. To ensure that cancer patients are identified only once, record linkage must create a single record for a patient who has, for example, 10 hoepitalization records, two pathology reports, a clinic registration and a death certificate. Because there is no unique personal identifying number on each health record in Ontario, several data elements are used to link a person's record. These are name, date of birth, OHIP number, residence and others depending upon the particular data source. Questionable links with neither very high nor very low weights are inspected manually to determine if these records pertain to the same or to different patients, and additional information usually is used to resolve these questionable links. Because of the number of different sources, a sequence of linkages must be performed (Fig. 3) before incident cases can be created.

TABLE VIII

Source Files Used to Create Ontario Cancer Incidence Data

DATA SOURCE	DESCRIPTION	NUMBER OF RECORDS PER YEAR
OHIP/HMRI	Hospital separations with a mention of cancer	100,000
Pathology	Pathology reports with a mention of cancer	35,000
Registration	Patients registered at the regional treatment centres and the Ontario Cancer Institute	18,000
Deaths	All deaths in Ontario residents	80,000
Incidence	All records on all patients diagnosed in the province 1964-1971	150,000

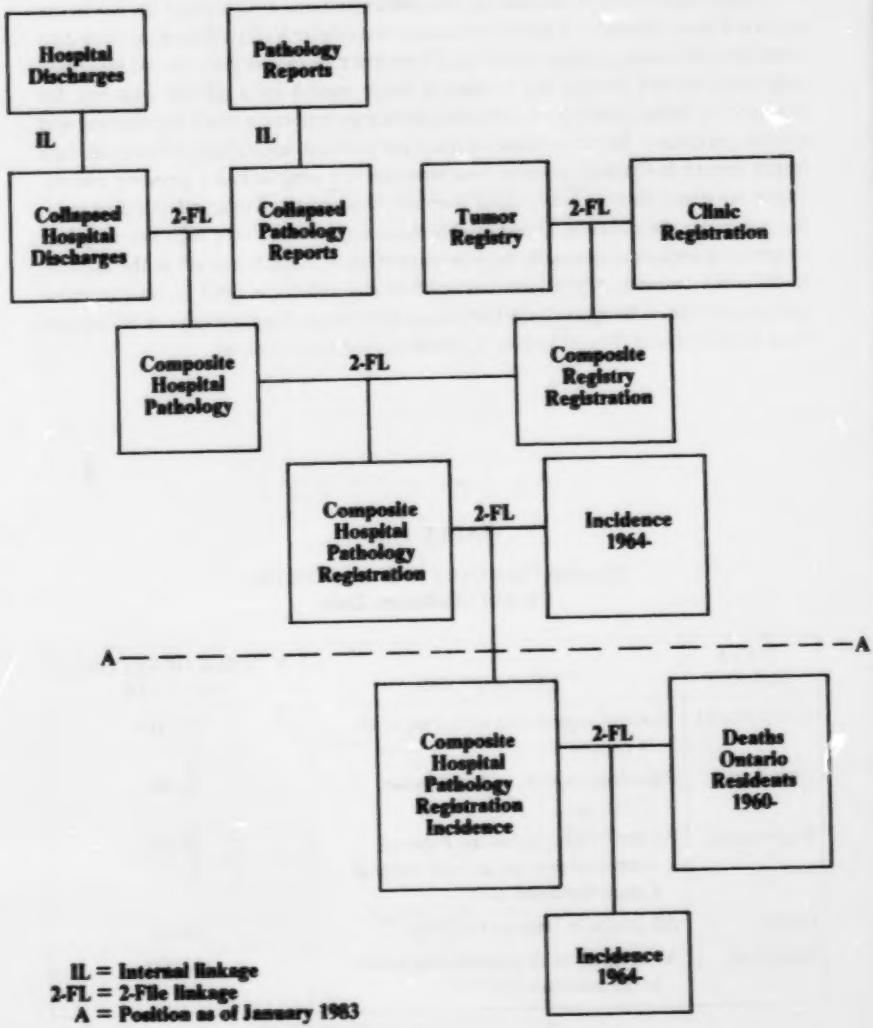

Fig. 3. Flow diagram showing linkage steps of Information System used to create cancer incidence data for Ontario.

The production of incidence data for the years 1972-1976 has been delayed for a number of reasons. Primarily, it was resolved to recreate the original source records from 1960-1971, which had been summarized during their transfer to a minicomputer in 1977. This "archival" file of more than one million records has not only been recreated but has undergone detailed computer and manual editing with the result that considerably more identifying information is available on each record. This additional information will permit a more rapid and accurate linkage with data from more recent years. Secondly, the Generalized Iterative Record Linkage System (GIRLS), developed at Statistics Canada in collaboration with the Epidemiology Unit of the National Cancer Institute of Canada, has been transferred to the Leaside Data Centre of the Ministry of Government Services. At the time of writing, we are at point A in Fig. 3, linking the composite hospital/pathology/registration data from 1972 to 1976 with the incidence data from 1964 onwards.

Additional resources would facilitate rapid generation of incidence data, because source information for the more recent years is available in machine-readable form at the Foundation; however, we have neither the personnel nor the funds to proceed with the linkages of the more recent data until the present linkages are complete. It would be possible to estimate incidence data for rare sites or for children from the source file by manual linkage of records: if there were a specific need for such information and if resources were provided, such estimates could be made.

Work is in progress to develop a new registry system for data beyond 1981, which will be generated on the Foundation's in-house computer. When this system is operational, the source information will be processed and linked as soon as it becomes available, and incidence data from Ontario then will be current with those from the rest of Canada.

Despite the limitations of the registry, it has been possible for the Division to participate, together with other cancer registries throughout the world, in collaborative studies with the International Agency for Research on Cancer. One such new study which may be initiated in the coming year is a review of second malignancies occurring in patients with Hodgkin's disease, and cancer of the testis or ovary treated by chemotherapeutic agents.

CANCER TREATMENT

Hospital Caseload

During the Ministry of Health's fiscal year 1980-1981, there were 65,023 separations (discharges and deaths) from active and rehabilitation hospitals in Ontario in which the primary diagnosis was cancer. These accounted for 5.1% of all hospital separations and 982,655 days of hospital care. The average length of stay for cancer patients declined from 19.8 days in 1970 to 15.5 days in 1980-1981.*

New Cancer Cases Registered at the Foundation Treatment Centres

In the last decade the number of new cases registered for the first time at the Foundation treatment centres has increased by 46% from 11,938 to 17,446 (Table IX). To make this comparison over time, it has been necessary to take into account the introduction of the Ninth Revision of the International Classification of Diseases in 1979. In addition, the Foundation returned, in 1981, to the international practice of counting patients with skin cancer as having only two lesions — a basal cell or a squamous cell cancer — and not as having multiple cancers. The distribution by clinic of these multiple skin lesions in 1981 is shown in Table X.

In Table X, for 1981, the major sites of newly registered cancers were lung, bronchus and trachea (15.7%) and breast (15.5%) followed by skin other than malignant melanoma (11.8%). Of the 16,044 patients seen for the first time at one of the treatment centres, 14.2% were seen in Hamilton; 5.2% in Kingston; 13.4% in London; 13.0% in Ottawa; 2.8% in Thunder Bay; 3.0% at Toronto-Bayview; 5.2% in Windsor; and 43.2% at the Princess Margaret Hospital, Toronto. It should be noted that these newly registered cases are new to the treatment centres, but are not necessarily newly diagnosed. (Fewer than 10% of all cases are recurrent and the proportion of recurrent cases varies by site of disease.)

The location of the regional treatment centres and the associated peripheral clinics determines the referral pattern to each centre (Table XI). Thus, of the 383 residents of Waterloo County referred to the Foundation, 52 were referred to the Hamilton Clinic, 266 to the London CLinic, 61 to the Princess Margaret Hospital and 4 to the Toronto-Bayview Clinic. In addition to Ontario residents, 410 residents of Quebec were referred to the Foundation centres, the majority of these being seen at the Ottawa Clinic. An additional 104 residents of other provinces were seen at the Foundation centres, mainly at the Princess Margaret Hospital. Of the 134 residents of the United States and other countries, 72 were referred to the Princess Margaret Hospital.

This past year, it has been difficult to maintain uniformity of the records at the regional treatment centres and the Princess Margaret Hospital due to the implementation of changes in the information systems of both institutions. During 1981, both old and

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*Hospital Statistics 1979/80 published by the Ministry of Health.

TABLE IX

New Cancer Cases Registered by Treatment Centre, 1972-1981[1,2]

CENTRE	YEAR OF REGISTRATION									
	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981
Hamilton	1,613	1,890	1,890	2,091	2,254	2,353	2,493	2,594	2,507	2,537
Kingston	921	932	887	921	816	988	1,040	999	984	997
London	1,988	2,111	2,254	2,359	2,460	2,344	2,488	2,537	2,583	2,529
Ottawa	1,363	1,423	1,502	1,525	1,631	1,759	1,902	1,997	2,078	2,190
Thunder Bay	236	300	313	313	399	365	412	369	401	462
Toronto-Bayview	—	—	—	—	—	—	—	—	441	504
Toronto, PMH	5,057	5,083	5,569	6,027	6,158	6,462	6,960	6,911	7,057	7,320
Windsor	760	770	857	889	880	843	854	898	813	907
TOTAL	11,938	12,509	13,272	14,125	14,598	15,114	16,149	16,305	16,864	17,446

[1] Excludes carcinoma of cervix in situ.

[2] Any case registered at more than one treatment centre in a given year is allocated to the centre where it was first registered.

TABLE X

New Cancer Cases Registered by Site of Disease and Treatment Centre, 1981

SITE OF DISEASE	ICD9[1] Number	TREATMENT CENTRE								TOTAL	
		Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	Number	Per Cent
							Bayview	PMH			
Lip	140	13	12	22	10	2	2	27	6	94	0.6
Tongue	141	14	5	25	8	–	11	80	10	153	1.0
Rest of mouth	142-145	38	12	29	38	3	21	127	8	276	1.7
Pharynx and tonsil	146-149	30	9	31	24	5	11	121	14	245	1.5
Esophagus	150	16	11	28	13	8	10	80	8	174	1.1
Stomach	151	47	5	20	39	9	9	76	16	221	1.4
Intestine, except rectum	152,153	100	24	80	152	10	21	225	52	664	4.1
Rectum and anal canal	154	116	18	83	74	9	7	260	39	606	3.8
Other digestive system	155-159	22	9	26	48	15	19	95	20	254	1.6
Nose, middle ear and accessory sinuses	160	5	1	10	3	1	1	36	3	60	0.3
Larynx	161	39	11	52	42	7	10	181	15	357	2.2
Lung, bronchus and trachea	162	308	150	279	351	64	85	1134	144	2515	15.7
Other respiratory	163-165	5	2	2	6	4	4	17	1	41	0.2
Bone	170	8	1	6	5	2	2	26	9	59	0.4
Malignant melanoma	172	71	15	46	44	9	84	155	14	438	2.7
Other cancer of skin	173	325	204	398	135	33	25	674	96	1890	11.8
Breast	174,175	334	93	308	395	81	48	1102	124	2485	15.5
Cervix uteri	180	53	28	48	60	13	–	204	13	419	2.6
Other uterus	179,181,182	96	21	108	84	15	1	228	29	582	3.6
Ovary, tubes and ligament	183	61	21	42	57	13	9	212	18	433	2.7
Other female genital organs	184	7	4	12	11	2	1	25	3	65	0.4
Prostate	185	91	41	88	83	19	14	280	37	653	4.1
Testis	186	17	3	23	19	4	–	82	5	153	1.0
Other male genital organs	187	2	1	3	2	–	–	6	–	14	0.1
Bladder	188	66	23	59	54	10	8	178	27	425	2.6
Kidney, other urinary	189	24	9	28	33	9	10	108	14	235	1.5
Brain and nervous system	191,192	37	10	46	45	9	25	181	11	364	2.3
Thyroid gland	193	22	1	8	4	2	1	43	2	83	0.5
Lymphosarcoma and reticulum-cell sarcoma	200	30	15	40	43	21	18	148	8	323	2.0
Hodgkin's disease	201	33	6	23	22	4	10	111	9	218	1.4
Other lymphomas	202	64	5	31	40	4	1	107	11	263	1.6
Leukemia	204-208	62	6	38	28	27	1	157	33	352	2.2
Other sites	Residual	126	52	106	115	28	15	453	35	930	5.8
TOTAL		2282	828	2148	2087	442	484	6939	834	16044	100.0
Cervix uteri (*in situ*)	233.1	3	2	3	4	1	–	5	2	20	–
Other sites (*in situ*)	230-234	28	17	48	24	2	18	84	8	229	–
Neoplasms of uncertain behaviour	235-238	36	2	12	6	–	2	64	11	133	–
Multiple skins (*see text*)	173	191	150	321	73	18	–	233	54	1040	–

[1]ICDA — International Classification of Diseases (Ninth Revision)

TABLE XI

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1981

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Algoma	1	1	5	–	–	2	130	1	140
Brant	161	–	5	–	–	–	16	–	182
Bruce	4	–	59	–	–	–	51	–	114
Carleton	1	1	–	1079	–	2	9	–	1092
Cochrane	4	–	2	9	2	3	133	–	153
Dufferin	2	–	–	–	–	3	30	–	35
Dundas	–	3	–	35	–	–	–	–	38
Durham[2]	–	–	–	1	–	15	332	–	348
Elgin	–	–	138	–	–	–	1	1	140
Essex	2	–	29	1	–	1	8	798	839
Frontenac	–	234	–	3	–	1	6	–	244
Glengarry	–	1	–	36	–	–	1	–	38
Grenville	–	29	–	35	–	–	2	–	66
Grey	4	–	49	–	–	2	117	–	172
Haldimand-Norfolk[3]	134	–	64	–	–	–	5	–	203
Haliburton	–	–	1	1	–	1	17	–	20
Halton	219	1	1	1	–	5	172	–	399
Hastings	–	170	–	4	–	–	80	–	254
Huron	–	–	109	–	–	–	3	–	112
Kenora	–	–	–	–	24	–	2	–	26
Kent	1	–	201	–	–	–	6	23	231
Lambton	–	–	225	–	–	–	–	1	226
Lanark	–	31	–	65	–	–	–	–	96
Leeds	–	137	–	1	–	1	4	–	143
Lennox and Addington	–	89	–	–	–	–	–	–	89
Manitoulin	–	–	–	–	–	–	16	–	16
Middlesex	3	–	613	–	–	–	6	1	623
Muskoka	1	–	–	–	–	2	77	–	80
Niagara[1]	530	–	4	–	–	11	152	–	697
Nipissing	–	–	–	5	–	–	168	–	173
Northumberland[2]	1	22	–	–	–	11	125	–	159
Oxford	4	–	166	–	–	–	6	–	176
Parry Sound	1	–	–	2	–	2	68	–	73
Peel	8	–	–	–	–	5	448	1	462
Perth	–	–	153	2	–	–	6	–	161

TABLE XI (Continued)

New Cancer Cases Registered by Place of Residence and Treatment Centre, 1981

COUNTY OR DISTRICT	TREATMENT CENTRE								TOTAL
	Hamilton	Kingston	London	Ottawa	Thunder Bay	Toronto		Windsor	
						Bayview	PMH		
Peterborough[2]	1	3	–	1	–	8	188	–	201
Prescott	–	–	–	47	–	–	–	–	47
Prince Edward	–	56	–	1	–	1	3	–	61
Rainy River	–	–	–	–	46	–	3	–	49
Renfrew	–	3	–	187	–	–	10	–	200
Russell	–	–	–	41	–	–	–	–	41
Simcoe[2]	1	–	–	–	–	9	404	–	414
Stormont	–	16	–	131	–	–	1	–	148
Sudbury	–	–	–	2	–	1	236	–	239
Thunder Bay	–	–	–	1	370	1	23	–	395
Timiskaming	–	1	1	1	–	6	89	–	98
Victoria[2]	2	1	1	–	–	10	109	–	123
Waterloo	52	–	266	–	–	4	61	–	383
Wellington	160	–	39	–	–	2	55	–	256
Wentworth	965	–	–	–	–	1	9	–	975
York	4	2	1	1	–	355	3380	3	3746
Quebec	1	1	–	383	–	4	20	1	410
Other Provinces	9	1	1	7	–	6	79	1	104
U.S.A.	5	25	14	1	–	2	16	2	65
Other	1	–	1	3	–	7	56	1	69
TOTAL	2282	828	2148	2087	442	484	6939	834	16044

[1]In 1971 the counties of Welland and Lincoln became the Regional Municipality of Niagara.

[2]In 1974 the counties of Durham and Ontario became the Durham Regional Municipality. Also the counties of Simcoe, Peterborough, Northumberland and Victoria have been expanded by parts of Durham and Ontario.

[3]In 1974 the counties of Haldimand and Norfolk became the Regional Municipality of Haldimand-Norfolk.

new systems have been in operation, which has put an additional burden on the medical record staff in the clinics and in the Division. It is anticipated that the new patient care management system will be fully operational in 1983. All concerned with the changeover from one system to the other are to be congratulated for their patience and forebearance during the last year.

Survival

The Division, with the assistance of Dr. Winifred M. Ross, radiation oncologist at the Kingston Clinic, prepared a review of the Ontario experience for the 22nd Clinical Conference in Kingston on colorectal cancer held in October 1982. The principal finding was the low proportion of incident cases of colorectal cancer referred to the Foundation treatment centres between 1969 and 1971. Only 8.5% of cancers of the colon, 9.4% of cancers of the rectosigmoid junction, and 15.3% of cancers of the rectum were referred to a regional treatment centre in the year of diagnosis. The proportion referred varied by age group, being greater in those under the age of 39 than among older patients. Between 1970 and 1979, 827 patients were referred to the Foundation with cancer of the colon, 1530 with cancer of the rectum and 742 with cancer of the rectosigmoid junction. These last were reviewed in more detail: 49% presented with metastatic disease and a further 12% could not be staged due to insufficient information. Of the remainder, the majority were classified as Astler Coller Stage B2 or C2. Both age and stage were prognostic factors, and adjuvant therapy was associated with improved survival.

Seminars in Cancer Epidemiology

In 1982, the Foundation held three epidemiology seminars to provide a forum for the discussion of issues in cancer epidemiology. The subjects were: "Breast Cancer Mortality Following Multiple Fluoroscopies: The Canadian Experience – 1950 to 1977" (Dr. G. R. Howe); "Descriptive and Experimental Studies of Colon Cancer" (Drs. W. R. Bruce, E. Bright-See, G. Eyssen, J. Heddle, and J. Krepinsky); "Mortality Studies in Nickel Workers" (Dr. H. Shannon and Mr. J. Julian).

ACKNOWLEDGEMENTS

The continuing co-operation of government is gratefully acknowledged; the Ontario Ministry of Health has provided source records and advice; the Office of the Registrar General of the Ministry of Consumer and Commercial Relations has

provided computerized data on deaths due to all causes in Ontario residents and, in addition, has undertaken a large number of death searches for treatment evaluation and research purposes. The assistance of Statistics Canada and the Epidemiology Unit of the National Cancer Institute of Canada in the preparation of incidence data for Ontario is greatly appreciated.

Our personal thanks are due to all the directors of the regional treatment centres and the Princess Margaret Hospital and their medical records officers for their support during the year, and to the members of the Foundation's Committee on Records and Statistics and the sub-committees.

We acknowledge with gratitude the assistance of all the staff of Information Systems in the processing of the Foundation's large data base, particularly the processing of the material for this report, which was done during the registry conversion phase.

Special thanks are extended to Mrs. Mary Nemes, Head of Medical Records in the Division, for her help in the preparation of this report, and to the staff of the Division, including the Research Unit at the University of Toronto, for the combination of statistical and clerical skills required for its completion.

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APPENDIX A

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The Foundation was the grateful recipient of legacies, bequests and other donations totalling $1,481,577 in 1981, which are of inestimable value to the Foundation's program.

Legacies of $1,000 or over were received from the following estates:

The late Lillian Maud Abbott, Toronto	$ 2,000.00
— Pearl Bingham, Cambridge	40,000.00 (part)
— Mary Hilda Blackwell, Hamilton	37,500.00 (part)
— John Carl Bodfish, Aurora	9,476.24 (part)
— Sophie Bolter, Toronto	2,000.00
— Grace Marion Brown, Ottawa for education and research	20,000.00
— Velma Elizabeth Brown, Newmarket	2,166.48
— John Sidney Burton, London for research at London Clinic	76,500.00 (part)
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— Reverend Susan Kathleen Christopher, Ottawa	69,678.58
— Christina Isabel Connell, Omemee	18,203.83
— Michael Joseph Costello, Ottawa	3,000.00
— Alberta McNab Daly, Toronto	1,420.00 (part)
— Eldred Durham, Toronto, (Ann and Eldred Durham Trust Fund) for research	7,973.59 (part)
— Doris Margaret Esdale, Ottawa	20,000.00 (part)
— Alice B. Fenner, Newmarket	17,086.11
— Laura Eva Freeman, St. Thomas	3,000.00
— Veronica Keith Gordon, Toronto	1,392.89 (part)
— Edna Gormley, Essex	10,366.80
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— Gwendolyn Gladys Humphreys, Brampton for research	5,000.00

— Susan Watson Jackson, Hamilton	21,395.50
— James Hawley Jenner, London for use at London Clinic	6,000.00 (part)
— R. Omar Kilburn, St. Thomas for use at London Clinic	1,000.00
— Alfred LeCours, Hearst	5,000.00
— Albert E. LePage, Toronto	1,985.96 (part)
— Erla M. Lovering, Toronto	18,750.00 (part)
— Mary I. Malloney, Toronto	85,200.00 (part)
— Hazel W. Mathewson, Toronto	5,000.00
— John Stanley Meredith, London (Jessie Meredith Memorial Trust Fund) for cancer research	39,014.45 (part)
— Henrietta Moody, Palermo for research	1,000.00
— Lyle E. Nesbitt, Toronto	1,580.16 (part)
— Laura E. Nichol, Wingham	18,693.98
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— Wilfred Lawson Ralph, Elizabethtown Township, for research	10,000.00
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— Bertha M. Richter, London (Richter Endowment Fund Trust) in memory of Martha Ann Richter and George Richter, for use at London Clinic	130,000.00 (part)
— Donald Cameron Routledge, London for research at London Clinic	42,300.00 (part)
— Cora Irene Russell, Richmond Hill	7,562.50 (part)
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— Mary Elva Sowers, London for use at London Clinic	1,000.00
— Ruth Stalker, Toronto	11,652.95 (part)
— Dorothy A. Standing, Toronto for research	90,000.00 (part)
— Michael Starchuk, Windsor	20,000.00
— Louis Szel, Toronto for research	10,950.00 (part)

— Elizabeth Taylor, Orillia	30,357.32 (part)
— Edward C. Watson, Ottawa for use at Ottawa Clinic Civic Hospital Division	20,000.00 (part)
— John White, Hamilton	10,000.00 (part)
— Madeleine Wilson, St. Mary's for research at London Clinic	1,409.11 (part)
— Leila Merle Young, St. Mary's	1,000.00

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— The Acklands Group, Toronto for research at Toronto-Bayview Clinic	$ 5,000.00
— Anonymous	1,000.00
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— Mr. George Stranak, Kingston for research at Kingston Clinic	13,000.00
— Thunder Bay South Jaycettes, Thunder Bay for use at Amethyst House	1,000.00
— The Toronto Star, Toronto	1,000.00
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— Mr. W. G. M. Wilson, London for the Harold E. Johns Summer Studentships in Medical Physics Program	2,500.00
— Mr. George Winter, Mount Brydges for research	2,500.00

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APPENDIX B

LIST OF ARTICLES PUBLISHED 1981

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